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323. *The Formation of Aromatic Hydrocarbons at High Temperatures. Part V.* The Pyrolysis of 1-Phenylbuta-1 : 3-diene.*

By G. M. Badger and T. M. Spotswood.

Pyrolysis of 1-phenylbuta-1 : 3-diene at 700° yields naphthalene, diphenyl, fluoranthene, phenanthrene, triphenylene, 1 : 2-benzanthracene, 9-phenylphenanthrene, 2(?)-phenylphenanthrene, 4(?)-phenylphenanthrene, chrysene, 3 : 4-benzofluoranthene, and 3 : 4-benzopyrene. Mechanisms for their formation are suggested.

The wide occurrence of 3 : 4-benzopyrene and of other carcinogenic hydrocarbons in smoke, soot, tar, and other similar materials has been clearly established. The mode of formation of 3 : 4-benzopyrene at high temperatures is therefore of some importance and a mechanism has been tentatively advanced.[1] It was suggested that this molecule may be built up from relatively simple components, and a detailed analysis of the tar formed by the pyrolysis of styrene has already been reported.[2] As a further contribution, the pyrolysis of 1-phenylbuta-1 : 3-diene has been undertaken.

The pyrolysis was carried out by passing phenylbutadiene vapour, with nitrogen, through a silica tube filled with porcelain chips, at 700°. Much of the material was decomposed to gaseous products, among which only methane and ethylene have been identified with certainty. These compounds, together with hydrogen, seem to be formed in nearly all pyrolyses of hydrocarbons, regardless of their structure, and their presence therefore gives little indication of the mechanism. The tar which was also obtained (in 29% yield) was collected and analysed by chromatography on alumina, gas-liquid partition chromatography, chromatography on acetylated paper,[3] and by spectroscopy. The following compounds were identified in this tar (% by wt. in parentheses): Naphthalene (67·2), diphenyl (5·2), fluoranthene (3·7), phenanthrene (13·3), triphenylene (0·83), 1 : 2-benzanthracene (0·89), 9-phenylphenanthrene (0·13), 4(?)-phenylphenanthrene (0·15), 2(?)-phenylphenanthrene (0·29), chrysene (1·33), 3 : 4-benzofluoranthene (0·78), 3 : 4-benzopyrene (0·12), " compound I " (0·41).

Naphthalene was the only substance identified by Liebermann and Ruber[4] following pyrolysis of phenylbutadiene in a glowing tube. No unchanged material could be detected, a fact of some importance. A C_6–C_4 substance has been postulated[1] as an intermediate in the conversion of acetylene, of butadiene, and of styrene into 3 : 4-benzopyrene. Phenylbutadiene is a typical C_6–C_4 compound, but this was not detected among the products of the pyrolysis of styrene.[2] However, it seems clear from the present work that phenylbutadiene is too readily decomposed, or cyclised, to survive a pyrolysis, and its absence from the products of pyrolyses of acetylene, butadiene, styrene, and similar compounds is not unexpected.

It is generally accepted that the reactions involved in the pyrolysis of hydrocarbons are predominantly radical in nature, and the products formed in pyrolysis of styrene at 710° can be satisfactorily explained on this basis.[2] Radicals have been detected by mass spectrometry in the pyrolysis of a number of aromatic compounds,[5] and the presence of the benzyl radical has been conclusively demonstrated[6] in the photolysis of toluene and ethylbenzene.

* Part IV, *J.*, 1958, 2458.

[1] Badger, Buttery, Kimber, Lewis, Moritz, and Napier, *J.*, 1958, 2449.
[2] Badger and Buttery, *J.*, 1958, 2458.
[3] Spotswood, *J. Chromatography*, 1959, **2**, 90.
[4] Liebermann and Ruber, *Ber.*, 1902, **35**, 2696.
[5] Ingold and Lossing, *Canadian J. Chem.*, 1953, **31**, 30; Lossing, Ingold, and Henderson, *J. Chem. Phys.*, 1954, **22**, 621; Farmer, Lossing, Marsden, and McDowell, *J. Chem. Phys.*, 1956, **24**, 52; Steacie, " Atomic and Free Radical Reactions," 2nd edn., Reinhold, New York, 1954.
[6] Porter and Wright, *Trans. Faraday Soc.*, 1955, **51**, 1469.

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The bond-dissociation energies for the carbon–hydrogen bonds in phenylbutadiene have not been determined, but by analogy with other compounds it seems likely that scission should occur preferentially as indicated by reaction (1). Cyclisation of the phenylbutadiene radical would then give naphthalene. The same compound could conceivably arise by direct cyclisation of phenylbutadiene with elimination of a molecule of hydrogen. In any case, naphthalene would be expected as a major product, and this has been found experimentally.

$$Ph{\cdot}CH{:}CH{\cdot}CH{:}CH_2 \longrightarrow Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot} + {\cdot}H \quad \ldots\ldots\ldots (1)$$

$$Ph{\cdot}CH{:}CH{\cdot}CH{:}CH_2 \longrightarrow Ph{\cdot} + {\cdot}CH{:}CH{\cdot}CH{:}CH_2 \quad \ldots\ldots\ldots (2)$$

$$Ph{\cdot}CH{:}CH{\cdot}CH{:}CH_2 \longrightarrow Ph{\cdot}CH{:}CH{\cdot} + {\cdot}CH{:}CH_2 \quad \ldots\ldots\ldots (3)$$

Carbon–carbon single bonds are known to have much smaller dissociation energies than carbon–carbon double bonds,[7] and with phenylbutadiene there are two single bonds in the side chain which could be broken. The bond orders have accordingly been determined by the M.O. method and the values are $Ph \overset{1\cdot437}{} CH{=}CH \overset{1\cdot477}{} CH{=}CH_2$. These orders indicate that there may be very little difference in the bond-dissociation energies of the two single bonds in the diene side chain. Nevertheless, the bond between the aromatic nucleus and the side chain does have a lower order, and it may be tentatively concluded that scission of this bond would be preferred, leading to reaction (2). The alternative scission to a styrene radical and an ethylene radical (reaction 3) would also be expected. However, this reaction cannot be of major importance for, if it were, the products of pyrolysis would be similar to those obtained from styrene [2] and this is not the case. For example, no dibenzyl, stilbene, toluene, or styrene could be detected.

The validity of this approach in establishing the nature of the radical fragments formed at high temperatures may be questioned. At the high temperatures involved many of the molecules will be in an excited state and the calculated bond orders may be meaningless. Nevertheless, on this basis, the major initial components of the pyrolysis would be: naphthalene, Ph·, $Ph{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}$, $CH_2{:}CH{\cdot}CH{:}CH{\cdot}$, and hydrogen, and the other products identified in the resulting tar can all be accounted for by secondary reactions involving these initial products.

Diphenyl could be produced by a chain-propagating reaction involving a phenyl radical and a phenylbutadiene molecule, or by a chain-terminating reaction involving two phenyl radicals. It may be noted that diphenyl is a product of the thermal [8] and photochemical [9] decomposition of tetraphenyl-lead, and it is also formed by the action of sodium on bromobenzene.[10] In all these cases a recombination of phenyl radicals seems probable.

In recent years the reaction of radicals with aromatic hydrocarbons has received some attention. With methyl radicals [11] the logarithms of the rate constants for reactions with different hydrocarbons are linearly related to the minimum localisation energies for the probable positions of attack in these molecules. Similar relationships have been derived for the positions of maximum free valency, for the singlet–triplet excitation energies, and for the polarographic half-wave reduction potentials.[12] Naphthalene, diphenyl, pyrene, and anthracene have already been shown to undergo radical attack at the positions of maximum free valency or lowest atom localisation energy.[13] In the present experiments, therefore, it seems likely that the aromatic hydrocarbons formed will also undergo attack by radicals and that the preferred positions of attack will be those of maximum free valency

[7] Braude and Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, New York, 1955; Szwarc, *Chem. Revs.*, 1950, **47**, 75.
[8] Dull and Simons, *J. Amer. Chem. Soc.*, 1933, **55**, 3898, 4328.
[9] Leighton and Mortensen, *J. Amer. Chem. Soc.*, 1936, **58**, 448.
[10] Horn and Polanyi, *Trans. Faraday Soc.*, 1934, **30**, 199; *Z. phys. Chem.*, 1934, *B*, **25**, 151.
[11] Szwarc, *J. Phys. Chem.*, 1957, **61**, 40.
[12] Matsen, *J. Chem. Phys.*, 1956, **24**, 602.
[13] Davies, Hey, and Williams, *J.*, 1958, 1878; Cadogan, Hey, and Williams, *J.*, 1954, 794; Norman, Thompson, and Waters, *J.*, 1958, 175; Beckwith and Waters, *J.*, 1957, 1001.

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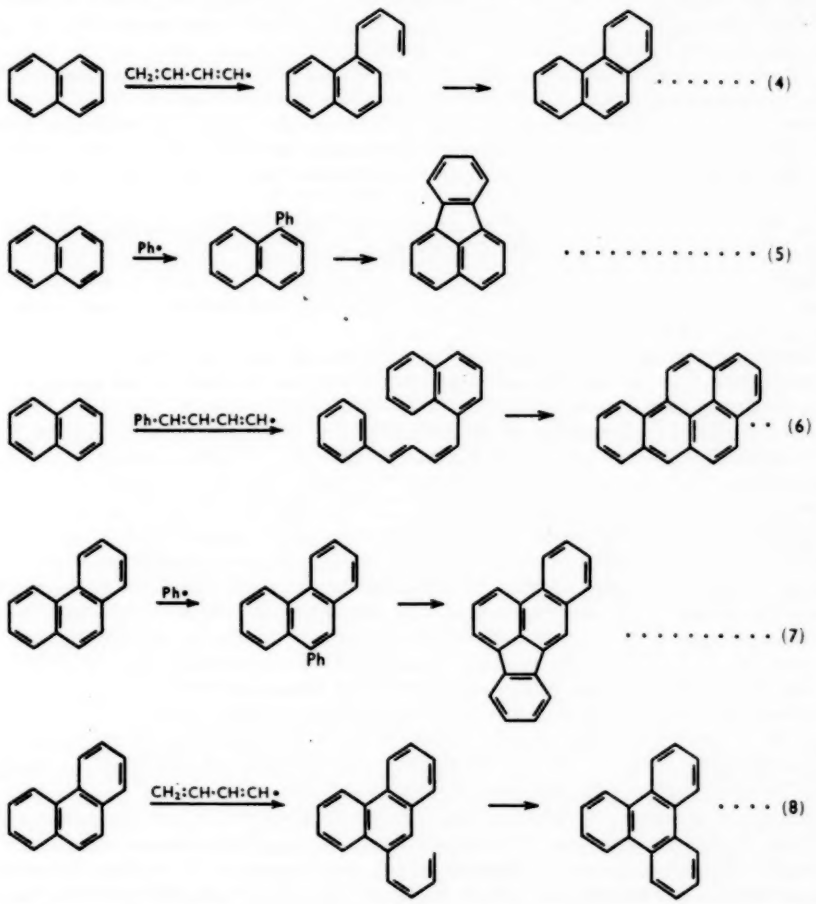
and minimum localisation energy. However, at the high temperature involved a proportion of the molecules may react in an excited state and the positions of substitution may not be as specific as expected from the differences in the localisation energies.

Thus, attack by a butadienyl radical at the 1-position of naphthalene, followed by cyclisation, would give phenanthrene (reaction 4), and this is a major product of the pyrolysis. Similar attack at the 2-position of naphthalene, followed by cyclisation, would also give phenanthrene and perhaps some anthracene. The latter has not been detected, but its absence is not significant in view of its known tendency to undergo further reaction at high temperatures.[14]

Attack by phenyl radicals on naphthalene would be expected to yield 1-phenylnaphthalene as the major product. This hydrocarbon was not identified in the tar, but



it is known to undergo cyclodehydrogenation to fluoranthene,[15] and this substance was present in relatively large amount (reaction 5). A small amount of 2-phenylnaphthalene might also be expected by this process, but was not detected. Its absence is noteworthy,

[14] Kinney and Debel, *Ind. Eng. Chem.*, 1954, **46**, 548.
[15] Orchin and Reggel, *J. Amer. Chem. Soc.*, 1947, **69**, 505.

for it was a major product of the thermal decomposition of styrene,[2] but in the latter case its presence can be explained by a different mechanism.

In the same way the attack of a phenylbutadienyl radical at the 1-position of naphthalene, followed by *cyclo*dehydrogenation of the product, would be expected to give 3 : 4-benzopyrene (reaction 6), which was also identified in the tar. This reaction was postulated in Part I of the present series.[1] Cyclisations of this type are certainly known to occur [16] and cyclodehydrogenation of 1-4′-phenylbutylnaphthalene has been shown to yield 3 : 4-benzopyrene and other products.[17]

Phenanthrene is formed in relatively large amount in the present pyrolysis, so that attack by radicals on this hydrocarbon might also be expected. It seems likely that the 9-position would be the preferred position for attack. However, calculation of the atom localisation energies for the various positions in phenanthrene, by Dewar's simplified method,[18] shows that the differences between these positions are considerably less than that between the 1- and the 2-position of naphthalene.

Attack by phenyl radicals would therefore give 9-phenylphenanthrene and perhaps other phenylphenanthrenes. 9-Phenylphenanthrene has been conclusively identified, as well as 3 : 4-benzofluoranthene which could arise from it by cyclodehydrogenation (reaction 7). Two other phenylphenanthrenes were also detected. These are provisionally regarded as the 2- and the 4-isomer, but their orientation has not been established beyond doubt.

In the same way, substitution of phenanthrene by butadienyl radicals followed by cyclisation of the various products would yield triphenylene (reaction 8), chrysene, 1 : 2-benzanthracene, and 3 : 4-benzophenanthrene. With the exception of 3 : 4-benzophenanthrene (which has a non-planar structure and is doubtless less stable), all these compounds have been identified in the tar.

These mechanisms offer a coherent explanation for the formation of the observed products, but they do not exhaust the possibilities and alternative mechanisms could occur simultaneously with the above.

In a study of the cracking of hydrocarbon oils, Weizmann *et al.*[19] suggested that condensation may be effected by a Diels–Alder addition of a butadiene molecule to aromatic hydrocarbons, followed by dehydrogenation. However, this type of mechanism cannot satisfactorily explain all the present results. On the basis of a Diels–Alder addition, the aromatic bond having the lowest bond localisation energy (or highest bond order) should be involved. The 9 : 10-bond of phenanthrene is known to have pronounced double-bond character, and Diels–Alder addition of butadiene to phenanthrene would be expected to give triphenylene as the major product. In fact, however, this is not formed in large amount. Moreover, it is very difficult to explain the formation of fluoranthene and 3 : 4-benzofluoranthene on Weizmann's theory, as no acenaphthene could be detected.

For the present purpose the mechanism of the formation of 3 : 4-benzopyrene is of paramount importance. If a Diels–Alder addition mechanism is assumed, then butadiene would have to react with pyrene, and both 3 : 4- and 1 : 2-benzopyrene would be expected. It is noteworthy, however, that neither pyrene nor 1 : 2-benzopyrene could be identified in the tar resulting from the pyrolysis of phenylbutadiene.

Authentic specimens of most of the compounds identified in the present tar were available for direct comparison of retention times (in gas–liquid chromatography), of R_F values (in chromatography on acetylated paper), and of spectra. 3 : 4-Benzofluoranthene was, however, synthesised by dehydrohalogenation of 9-(2′-chlorobenzylidene)fluorene with potassium hydroxide in quinoline.

The bond orders in phenylbutadiene have been calculated by the molecular orbital

[16] Hansch, *Chem. Revs.*, 1953, **53**, 353; Cook and Robinson, *J.*, 1940, 303.
[17] Badger and Kimber, *J.*, 1958, 2455.
[18] Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3341.
[19] Weizmann *et al.*, *Ind. Eng. Chem.*, 1951, **43**, 2312, 2318, 2322, 2325.

method. Previous calculations[20] on this molecule have been confined to the determination of the energy levels of the orbitals. The eigenvalues and the eigenvectors of the secular matrix have now been determined by the usual methods, equal Coulomb and resonance integrals being assumed, and overlap neglected, and the bond orders calculated from the relationship

$$p_{rs} = \sum_j n_j c_{rj} c_{sj}$$

The resonance energy is found to be 2·9323β.

Experimental

Pyrolysis of 1-*Phenylbuta*-1 : 3-*diene at* 700°.—1-Phenylbuta-1 : 3-diene[21] (n_D^{20} 1·6070; 70 g.) was vaporised at 7 g./hr. in a flash-evaporator (kept at 400°) and carried with a stream of nitrogen (1 c.c./sec.) through a silica tube (40″ × ¾″ internal diam.) packed with porcelain chips (¼″—½″), kept at 700°.[1] The product was a semi-solid mass (18 g.), but carbon (3 g.) was deposited in the tube and there was a non-volatile residue (3 g.) in the evaporator. The remainder of the material appeared in the exit gases, which burnt with a luminous flame.

The product gave no distillate when heated at 120°/18 mm. and was therefore chromatographed in hexane on a column (50 × 5 cm.) of type H activated alumina. Elution was with hexane followed by hexane–benzene mixtures containing increasing amounts of benzene. The 120 fractions collected were evaporated, and the residues chromatographed on acetylated paper, by the ascent method, ethanol–toluene–water (17 : 4 : 1, v/v) being used as developing solvent.[3] The positions of fluorescent compounds were determined by viewing the papers under ultraviolet light. After these spots had been marked, the papers were sprayed with 2% tetrachlorophthalic anhydride in acetone–chlorobenzene (10 : 1; v/v) and again examined under ultraviolet light. Under these conditions all the non-fluorescent compounds tested (with the exception of naphthalene and its simple derivatives) gave bright yellow or orange spots. Some weakly-fluorescent compounds also gave yellow spots, and a number of the more strongly fluorescent compounds (*e.g.*, pyrene and perylene) gave orange spots after prolonged heating of the sprayed paper. With these paper chromatograms as a guide the various fractions were then re-combined to give seven major fractions each of which was separately analysed.

Analysis of Exit Gases.—The infrared spectrum of the exit gases showed the presence of several hydrocarbons. Methane was positively identified from the characteristic band system around 1300 cm.$^{-1}$, and ethylene from that around 950 cm.$^{-1}$.

Analysis by Gas–Liquid Chromatography.—Fraction 1 was analysed in a Griffin and George vapour-phase chromatographic apparatus. The column was packed with Apiezon L supported on Celite (40—80 mesh, B.S.S.; 1 : 4, w/w), and kept at 180°. Nitrogen (1 l./hr.; inlet pressure, 41 cm.; outlet pressure, 0·5 cm.) was used as carrier gas. Peaks corresponding to naphthalene (retention time, 6·4 min.) and diphenyl (retention time, 14·2 min.) were obtained in agreement with the times for authentic specimens. The diphenyl was collected and identified by infrared spectroscopy (see below), and the percentage composition of the fraction was determined by calculating the ratio of the areas under the peaks.

Analysis by Chromatography on Acetylated Paper.—Fractions 2—7 were analysed by chromatography on acetylated paper by the technique already described.[3] The papers were developed with methanol–ether–water (4 : 4 : 1, v/v) by the ascent method. Fluorescent compounds were located by observation under ultraviolet light, and non-fluorescent compounds by spraying a strip cut from the chromatogram with tetrachlorophthalic anhydride (see above). Spots were then cut out and extracted with ether in a small Soxhlet apparatus, the extracts evaporated, and the residues dissolved in 95% ethanol for ultraviolet spectrographic examination. To obtain sufficiently intense spectra, several chromatograms were combined, and the concentration of the ethanolic solution adjusted to give suitable optical density readings. In some cases, in order to obtain good separations, it was necessary to develop the papers by the descent method, and to allow the solvent-front to over-run the end of the paper. In cases of particular difficulty (*e.g.*, the separation of 3 : 4-benzopyrene and 3 : 4-benzofluoranthene), the spots were cut out, and the extracts rechromatographed on acetylated paper, the descent method being used with extended development time.

[20] Syrkin and Diatkina, *Acta Physicochem. U.R.S.S.*, 1946, **21**, 641 (*Chem. Abs.*, 1947, **41**, 1648); Brown, *J. Amer. Chem. Soc.*, 1953, **75**, 4077.
[21] Grummitt and Becker, *Org. Synth.*, 1950, **30**, 75.

The percentage composition of each fraction was determined by calculating the weight present in each extract from the observed optical density at several wavelengths, and comparing them with the recorded extinction coefficients. Although the effect of background absorption is appreciable, the relative amounts of the components in a mixture could thus be determined with reasonable precision.

The results of the analysis of 12·5 g. of tar are summarised as follows: fraction 2 (1·5 g.), phenanthrene and fluoranthene; fraction 3 (0·5 g.), fluoranthene, phenanthrene, and triphenylene; fraction 4 (0·2 g.), triphenylene, fluoranthene, 1 : 2-benzanthracene, and 9-phenylphenanthrene; fraction 5 (0·24 g.), chrysene, 4(?)-phenylphenanthrene, 1 : 2-benzanthracene, 3 : 4-benzopyrene, 3 : 4-benzofluoranthene, and " compound I "; fraction 6 (0·18 g.), 3 : 4-benzofluoranthene, 1 : 2-benzanthracene, 3 : 4-benzopyrene, 2(?)-phenylphenanthrene, and " compound I "; and fraction 7 (0·1 g.), not identified.

Details of Identification.—Naphthalene. This was isolated from fraction 1 by repeated sublimation. It had m. p. 80°, not depressed by admixture with an authentic specimen.

Diphenyl. This was isolated after gas–liquid chromatography of fraction 1. After recrystallisation from ethanol it had m. p. and mixed m. p. 68—70°; $\nu_{max.}$ (in Nujol mull) 5·10, 5·25, 5·41, 5·50, 5·68, 5·82, 6·00, 6·12, 6·58, 7·21, 7·40, 7·60, 7·82, 8·42, 8·50, 8·61, 8·95, 9·12, 9·28, 9·58, 9·90, 11·08, 11·90, 12·80, 13·7, and 14·8 μ. An authentic specimen showed the same maxima, but the 12·80 μ maximum was less pronounced.

Fluoranthene. This was identified by comparison of its behaviour on acetylated paper with an authentic specimen. An extract prepared from paper chromatograms showed $\lambda_{max.}$ 236, 245, 262, 276, 287, 323, 342, and 360 mμ characteristic of fluoranthene,[22] and $\lambda_{max.}$ 257, 273, and 302 mμ due to traces of triphenylene.

Phenanthrene. Extracts of spots obtained in paper chromatograms showed $\lambda_{max.}$ 242, 251, 274, 280, 293, 318, 330, 336, and 346 mμ, in good agreement with recorded values for phenanthrene.[22] Repeated recrystallisation of fraction 3 from ethanol and chromatography of the product on alumina gave crystalline material, m. p. and mixed m. p. 99—101°.

Triphenylene. This was identified by comparison with an authentic specimen on acetylated paper. An extract showed $\lambda_{max.}$ 250, 257, 274, 286, 302, 316, 332, and 340 mμ, in good agreement with values in the literature.[22]

1 : 2-*Benzanthracene.* This was identified by comparison with an authentic specimen on acetylated paper. An extract showed $\lambda_{max.}$ 227, 254, 267, 277, 288, 300, 315, 326, 341, and 358 mμ, in good agreement with recorded values.[22]

9-*Phenylphenanthrene.* This was identified by comparison with an authentic specimen on acetylated paper. An extract showed $\lambda_{max.}$ 236 and 253 mμ with a point of inflexion at 296 mμ, in good agreement with the literature.[22]

4(?)-*Phenylphenanthrene.* An extract from a paper chromatogram showed $\lambda_{max.}$ 229, 237, 254, 270, 290, and 335 mμ. These values are in good agreement with those obtained from the curve given by Campbell [23] for this compound, and the shapes of the two curves were similar.

2(?)-*Phenylphenanthrene.* An extract from a paper chromatogram showed $\lambda_{max.}$ 258, 265, 292, 302, and 340 mμ. With the exception of the 340 mμ peak, these values are in good agreement with those recorded for 2-phenylphenanthrene; [22] but as this peak was retained even after further chromatography on acetylated paper its identification is in some doubt. 3-Phenylphenanthrene has not been described and its absorption spectrum may be similar to that of 2-phenylphenanthrene.

Chrysene. This was identified by comparison with an authentic specimen on acetylated paper. An extract showed $\lambda_{max.}$ 242, 258, 268, 283, 294, 306, 320, 344, 350, and 361 mμ, together with a point of inflexion at 333 mμ, in good agreement with recorded values.[22] Chromatography of fraction 5 on alumina, followed by repeated recrystallisation of the product from ethanol, gave chrysene, m. p. and mixed m. p. 253—254°.

3 : 4-*Benzofluoranthene.* This was identified by comparison with an authentic specimen on acetylated paper. An extract showed $\lambda_{max.}$ 238, 256, 266, 276, 290, 301, 320, 338, 350, and 369 mμ in good agreement with the recorded values [22] with the exception of the peak at 290 mμ which should show a double peak at 289 and 293 mμ.

3 : 4-*Benzopyrene.* Initial identification of this compound was made by comparison of the

[22] Clar, " Aromatische Kohlenwasserstoffe," 2nd edn., Springer-Verlag, Berlin, 1952; Friedel and Orchin, " Ultraviolet Spectra of Aromatic Compounds," Wiley, New York, 1951.
[23] Campbell, *J.*, 1954, 3659.

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fluorescence spectrum [1] of an extract from a paper chromatogram with that of an authentic specimen: the spectra were identical. The extract was twice rechromatographed on acetylated paper and an extract in 95% ethanol showed $\lambda_{max.}$ 254, 264, 273, 279, 284, 296, 347, 364, 384, and 404 mμ in good agreement with recorded values.[22] The identity of the compound was further confirmed by direct comparison with an authentic specimen on acetylated paper: 3 : 4-benzopyrene shows a highly characteristic intense violet fluorescent spot under ultraviolet light.

"*Compound* I." This compound showed a light blue fluorescence in solution and a yellow-green fluorescent spot on acetylated paper. An extract from a paper chromatogram showed $\lambda_{max.}$ 258, 262, 274, 288, 316, 331, 360, and 366 mμ with points of inflexion at 300, 340, and 350 mμ. This spectrum suggests a phenanthrene derivative, but the substance has not been positively identified.

Synthesis of 3 : 4-*Benzofluoranthene.*—The following procedure is adapted from that in the patent literature.[24] Fluorene (16 g.) was added to a solution of sodium ethoxide [from sodium (4 g.)] in ethanol (250 c.c.), and the mixture heated to 75°. *o*-Chlorobenzaldehyde (14 g.) in ethanol (100 c.c.) was added dropwise with shaking, and the mixture refluxed for 30 min. Ethanol (300 c.c.) was then removed under reduced pressure, and the residue poured into water (400 c.c.). The benzene (200 c.c.) extract was washed with water, dried ($MgSO_4$), and evaporated. Chromatography on alumina, and elution with hexane, gave a yellow oil, b. p. 180°/0·7 mm. Recrystallisation from methanol gave 9-(*o*-chlorobenzylidene)fluorene (9·2 g., 30%), m. p. 69—70°.

A mixture of this product (1 g.), potassium hydroxide (3 g.), and quinoline (10 c.c.) was refluxed for 90 min., cooled, and poured into concentrated hydrochloric acid (150 c.c.). The benzene (100 c.c.) extract was washed with water, dilute aqueous sodium carbonate, and water, then dried and evaporated. Chromatography on alumina and elution with hexane gave unchanged material (0·5 g.); further elution with benzene–hexane (1 : 2) gave 3 : 4-benzofluoranthene. After recrystallisation from ethanol it formed needles, m. p. 167° (210 mg.; 24%). Its benzene solution was strongly fluorescent and its ultraviolet absorption was identical with that recorded.[22]

This work has been carried out during the tenure of a grant from the Damon Runyon Memorial Fund. We are also grateful to Mr. A. G. Moritz for the infrared spectra.

UNIVERSITY OF ADELAIDE, SOUTH AUSTRALIA. [*Received, September 8th,* 1958.]

[24] B.P. 459,108; *Chem. Abs.*, 1937, **31**, 4136.

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324. *The Quinoline Series. Part I. Addition Reactions of Quinaldine and Lepidine.*

By S. SKIDMORE and E. TIDD.

Quinaldine and lepidine have been added to activated olefinic systems in the presence of organic and inorganic acids as catalysts. The ease of addition is shown to depend upon the temperature of the reaction and the acid strength of the catalyst.

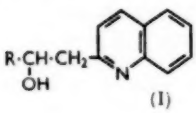
The ultraviolet absorption spectra of some of the addition compounds have been measured, and the formation and hydrolysis of their methiodides examined.

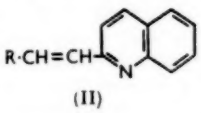
ALDEHYDES react with quinaldine to yield hydroxy-compounds (I), olefins (II), or diquinolylpropanes (III), depending upon the conditions employed.

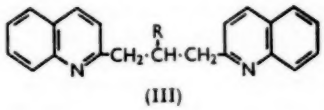
Koenigs [1] has shown that benzaldehyde and an excess of quinaldine at 150—160° in presence of anhydrous zinc chloride afford mainly the diquinolylpropane (III; R = Ph) which could be formed by condensation of quinaldine with the initially formed hydroxy-compound (I; R = Ph) or by addition of quinaldine to the olefin (II; R = Ph). It has

[1] Koenigs, *Ber.*, 1899, **32**, 3599.

now been found, however, that heating quinaldine with the hydroxy-compound at 100° with anhydrous zinc chloride or benzoic acid yields 2-styrylquinoline by dehydration, but no substituted propane. The alternative mechanism was then considered. Base-catalysed Michael-type additions of quinaldine and lepidine to activated olefinic systems


(I)


(II)


(III)

have been described by Weiss and Hauser [2] but very little work is recorded on acid-catalysed additions of these bases. Quinaldine or lepidine and 2-styrylquinolines with benzoic acid, a mineral acid, or anhydrous zinc chloride as catalyst, gave good yields of trisubstituted propanes depending upon the catalyst and temperature used (Table 1). No addition occurred at 100°, which would explain the absence of addition product in the attempted reaction between quinaldine and the hydroxy-compound (I; R = Ph). The separation of adducts from unchanged olefin was possible because of the greater solubility of the former in 0·1N-hydrochloric acid.

TABLE 1. *Addition of quinaldine to styrylquinoline.*

Effect of catalyst: 5 hr. at 135°.

Catalyst	BzOH	H_2SO_4	AcOH	*o*-HO·C_6H_4·CO_2H	HCl	HCl *
Product (III; R = Ph) (%)	0	82	0	0	82	82

* As hydrochloride of (II; R = Ph).

Effect of temperature: (*a*) BzOH for 5 hr.

Temp.	135°	140°	145°	150°	155°	166°
Product (III; R = Ph) (%)	0	12	21	67	70	73

(*b*) H_2SO_4 for 3 hr.

Temp.	100°	110°	120°	125°	130°	135°
Product (III; R = Ph) (%)	0	2	9	42	52	80

The addition reactions were extended to ethyl cinnamate and 4-styrylquinoline. The adduct from quinaldine and ethyl cinnamate gave an acid on hydrolysis which was identical with that isolated by Weiss and Hauser from their base-catalysed reaction. The adduct obtained from quinaldine and 4-styrylquinoline was identical with that obtained from lepidine and 2-styrylquinoline. Attempts to add lepidine to 4-styryl-quinoline gave colourless needles which could not be obtained with a sharp melting point and gave an unexpected analysis. Koenigs recorded a similar indistinct melting point for the compound which he isolated from the reaction between lepidine (2 mols.) and benzaldehyde (1 mol.).

Preparation of monomethiodides of the adducts as described by Hamer [3] yielded only dimethiodides. Hamer hydrolysed 2-phenyl-1 : 3-di-2′-quinolylpropane dimethiodide by boiling its aqueous solution and obtained 2-styrylquinoline methiodide. When a similar reaction was attempted using 2-phenyl-1 : 3-di-4′-quinolylpropane dimethiodide only unchanged material was recovered. The case of the dimethiodide of 2-phenyl-1-2′-quinolyl-3-4′-quinolylpropane was of interest since either 2- or 4-styrylquinoline methiodide could be produced. Prolonged hydrolysis of the substance yielded 4-styrylquinoline methiodide.

Spectra.—The ultraviolet absorption spectra of several substituted propanes described above have been determined (see Table 2). The general form of the curves can be interpreted as a result of the combination of the spectra of quinoline and a substituted toluene. The latter behaves as an insulated chromophore since no conjugation can occur between the benzene and quinoline nuclei.

[2] Weiss and Hauser, *J. Amer. Chem. Soc.*, 1949, **71**, 2023.
[3] Hamer, *J.*, 1923, **123**, 246.

TABLE 2. *Absorption spectra* (λ *in* mμ) *of* 2-R-1 : 3-*di*-2′-*quinolylpropane* (III).

R = Ph		R = *p*-C_6H_4Me		R = *m*-NO_2·C_6H_4		R = *p*-NO_2·C_6H_4	
$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε	$\lambda_{max.}$	log ε
267	3·89	269	3·89	265	4·11	261—275	4·14
290	3·70	291	3·69	~290	3·83		
297	3·67	297	3·66	297	3·78		
304	3·81	304	3·79	304	3·85	304	3·95
309	3·72	309	3·72	309	3·74	309	3·82
317	3·93	317	3·93	317	3·93	317	3·96

EXPERIMENTAL

1-*Phenyl*-2-2′-*quinolylethanol*.—Benzaldehyde (500 g.), a small amount of benzoic acid, and quinaldine (750 g.) were shaken together and set aside at room temperature. Precipitation occurred during several weeks and the precipitate was filtered off at 7 day intervals. The product was washed with light petroleum (b. p. 60—80°) and crystallised once from ethanol to give colourless needles (407 g., 34%), m. p. 127° (Benrath [4] gives m. p. 131°).

2-*Styrylquinoline*.—(*a*) 1-Phenyl-2-2′-quinolylethanol (100 g.) was dehydrated with acetic anhydride as described by Benrath, to give cream-coloured needles of 2-styrylquinoline (91·4 g., 98·5%), m. p. 100°.

(*b*) The method described by Jacobsen and Reimer,[5] starting from quinaldine and benzaldehyde, was used except that the catalyst was acetic anhydride and the reactants were kept at 125° during 2 hr. (68%).

Nitrostyrylquinolines.—Quinaldine (4·0 g.), *m*- or *p*-nitrobenzaldehyde (4·22 g.), and acetic anhydride (2·85 g.) were heated together in a sealed tube at 125° during 1 hr. The product was steam-distilled to remove unchanged quinaldine and aldehyde, the residue of nitrostyrylquinoline dissolved in the minimum quantity of hot ethanol, and the solution poured into water (250 ml.) with stirring. The precipitated base was removed and dried.

(*a*) 2-3′-Nitrostyrylquinoline (6·85 g., 89%), m. p. 149—151°, crystallised twice from benzene and once from ethanol to give pale yellow needles, m. p. 156° (Walton, Tipson, and Cretcher [6] give m. p. 157—158°).

(*b*) 2-4′-Nitrostyrylquinoline (7·04 g., 91%) formed needles (from ethanol), m. p. 169° (Walton *et al.* give m. p. 171—172°).

2-4′-*Methylstyrylquinoline*.—Quinaldine (4 g.), *p*-tolualdehyde (3·36 g.), and acetic anhydride (2·85 g.) were treated as described for nitrostyrylquinolines. The crude base crystallised from ethanol as pale yellow needles, m. p. 140° (1·49 g., 22%) (Found: C, 88·0; H, 6·2; N, 5·8. Calc. for $C_{18}H_{15}N$: C, 88·2; H, 6·1; N, 5·7%). von Grabski [7] described the preparation of this compound and its hydrochloride but did not record the m. p. of the free base.

4-*Styryl-lepidine*.—A procedure modified from that described by Kaslow and Stayner [8] was used. Lepidine (13·7 g.), benzaldehyde (18 g.), and anhydrous zinc chloride (1·6 g.) were heated together at 170° during 3 hr. The product was treated with 20% sodium hydroxide solution (30 ml.), and the viscous oil produced was washed with water by decantation. After 15 min. the oil solidified and was then filtered off and treated with concentrated hydrochloric acid (25 ml.). The yellow base hydrochloride which was precipitated was dissolved in hot water (1 l.), and the solution basified, cooled, and extracted with benzene (250 ml.). Filtering the benzene solution and shaking it with 2N-hydrochloric acid (200 ml.) precipitated a yellow hydrochloride, which was washed with 2N-hydrochloric acid, dissolved in warm water, and basified. The precipitated base was dried and crystallised from light petroleum (b. p. 80—100°), forming pale cream-coloured crystals (15·4 g., 70%), m. p. 88°.

On basification of the hydrochloric acid mother-liquors, a green oil was obtained which solidified (2·5 g.). Crystallisation from light petroleum (b. p. 100—120°) yielded colourless needles, m. p. 106—110°. The compound gave no colour with hydrochloric acid and was thought to be benzylidenedilepidine.

2-*Phenyl*-1 : 3-*di*-2′-*quinolylpropane*.—Quinaldine (9·3 g.), 2-styrylquinoline (5 g.), and

[4] Benrath, *J. prakt. Chem.*, 1906, **73**, 383.
[5] Jacobsen and Reimer, *Ber.*, 1883, **16**, 1082, 2602.
[6] Walton, Tipson, and Cretcher, *J. Amer. Chem. Soc.*, 1945, **67**, 1501.
[7] von Grabski, *Ber.*, 1902, **35**, 1957.
[8] Kaslow and Stayner, *J. Amer. Chem. Soc.*, 1945, **67**, 1716.

anhydrous zinc chloride (1 g.) were heated together in a sealed tube at 150—160° during 5 hr. The product was dissolved in hot N-hydrochloric acid (250 ml.) and then basified with aqueous sodium hydroxide. The precipitated bases were extracted with benzene and shaken with 2N-hydrochloric acid (200 ml.). Repeated trituration of the precipitated hydrochloride with 0·1N-hydrochloric acid and basification of the acid extracts yielded a brown gum (5·1 g., 63%). Crystallised from light petroleum (b. p. 80—100°), the base separated as white rosettes, m. p. 90—92° (Hamer reports 90—94°) (Found: C, 86·5; H, 6·1; N, 7·6. Calc. for $C_{27}H_{22}N_2$: C, 86·6; H, 5·9; N, 7·5%). The dimethiodide crystallised from ethanol–ether as pale yellow needles, m. p. 179° (Found: C, 52·3; H, 4·4; I, 37·4. Calc. for $C_{29}H_{28}N_2I_2$: C, 52·9; H, 4·3; I, 38·7%).

With benzoic acid or concentrated sulphuric acid in place of zinc chloride similar results were obtained.

2-m-*Nitrophenyl*-1 : 3-*di*-2′-*quinolylpropane*.—Quinaldine (8·6 g.), 2-3′-nitrostyrylquinoline (5·5 g.), and concentrated sulphuric acid (1·4 g.) were heated at 135° during 4 hr. The product was dissolved in hot 2N-hydrochloric acid, filtered from tar, and basified with aqueous sodium hydroxide. The precipitated bases were extracted with benzene and shaken with 2N-hydrochloric acid (200 ml.). The precipitated hydrochloride was dissolved in warm water and basified. The product (7·25 g., 86·6%), crystallised from light petroleum (b. p. 100—120°), gave 2-m-*nitrophenyl*-1 : 3-*di*-2′-*quinolylpropane* as colourless rosettes, m. p. 154° (Found: C, 77·6; H, 5·2; N, 9·8. $C_{27}H_{21}O_2N_3$ requires C, 77·3; H, 5·1; N, 10·0%). The *dimethiodide* had m. p. 202—204° (from ethanol–ether) (Found: C, 49·5; H, 4·1; I, 35·7. $C_{29}H_{27}O_2N_3I_2$ requires C, 49·5; H, 3·9; I, 36·1%).

2-4′-Nitrostyrylquinoline gave 2-p-*nitrophenyl*-1 : 3-*di*-2′-*quinolylpropane* (5·8 g., 69·3%), m. p. 165° [from light petroleum (b. p. 100—120°)] (Found: C, 77·2; H, 5·2; N, 10·3%) [*dimethiodide* (from ethanol), m. p. 201—203° (Found: C, 49·5; H, 3·9%)].

2-4′-Methylstyrylquinoline gave 1 : 3-*di*-2′-*quinolyl*-2-p-*tolylpropane* (5·2 g., 66·2%), which crystallised from benzene, light petroleum (b. p. 100—120°), or ethanol as colourless needles, m. p. 121° (Found: C, 86·6; H, 6·4; N, 7·3. $C_{28}H_{24}N_2$ requires C, 86·6; H, 6·2; N, 7·2%). Its *dimethiodide* had m. p. 201—203° (from ethanol) (Found: C, 54·5; H, 4·7. $C_{30}H_{30}N_2I_2$ requires C, 53·6; H, 4·5%).

2-*Phenyl*-1-2′-*quinolyl*-3-4′-*quinolylpropane*.—(*a*) *Addition of lepidine to* 2-*styrylquinoline*. Lepidine (7·2 g.) and 2-styrylquinoline hydrochloride (5·4 g.) were heated together at 135° during 5 hr. The product solidified. Treatment with 5N-hydrochloric acid yielded a red-brown solution which on cooling in ice gave no precipitate, indicating the absence of unchanged 2-styrylquinoline. Pouring the solution into an excess of ice-cold (15%) sodium hydroxide solution gave a green viscous base which was washed several times by decantation, then redissolved in 2N-hydrochloric acid, and 2N-sodium hydroxide was added until the solution remained faintly acid. A pale green, granular, precipitate became sticky after separation (5·1 g., 58·4%). Dissolving the base in ether and setting the solution aside yielded a granular *product* which crystallised from light petroleum (b. p. 60—80°) as colourless needles, m. p. 107—108° (Found: C, 85·9; H, 6·1; N, 7·6. $C_{27}H_{22}N_2$ requires C, 86·6; H, 5·9; N, 7·5%). The *dimethiodide*, crystallised from ethanol, had m. p. 175—176° (Found: I, 38·8; N, 4·4. $C_{29}H_{28}N_2I_2$ requires I, 38·7; N, 4·3%).

(*b*) *Addition of quinaldine to* 4-*styrylquinoline*. Quinaldine (1·86 g.), 4-styrylquinoline (1·0 g.), and concentrated sulphuric acid (0·28 g.) were heated together at 135—140° during 3 hr. The mixture was dissolved in 2N-hydrochloric acid (20 ml.), basified with aqueous sodium hydroxide, and freed from quinaldine by steam-distillation. The residue was dissolved in 2N-hydrochloric acid (20 ml.), cooled in ice-water, and set aside for 1 hr. The yellowish-brown deposit was filtered off, dissolved in water, and basified. The base was extracted with ether, and the ethereal solution dried (Na_2SO_4) and concentrated. The resulting viscous oil solidified overnight and crystallised from light petroleum (b. p. 60—80°) as needles (1·05 g., 65%), m. p. 107—108°, alone or mixed with the product from (*a*).

2-*Phenyl*-1 : 3-*di*-4′-*quinolylpropane*.—Lepidine (1·86 g.), 4-styrylquinoline (1·0 g.), and concentrated sulphuric acid (0·28 g.) were heated together at 135—140° during 3 hr. Working up as in the preceding case gave a solid base (1·32 g.) which on attempted crystallisation from light petroleum (b. p. 100—120°) yielded an oil. Shaking it with ether (10 ml.), however, afforded a white powder (0·5 g.) which gave no colour with N-hydrochloric acid and crystallised from light petroleum (b. p. 80—100°) as needles, m. p. 109—124° (Koenigs [1] gives 110—127°)

(Found: C, 82·4; H, 6·3; N, 6·7. Calc. for $C_{27}H_{22}N_2,H_2O$: C, 82·6; H, 6·2; N, 7·1%). The *dimethiodide*, crystallised from methanol, had m. p. 234—235° (Found: C, 52·8; H, 4·3; I, 38·4. $C_{29}H_{28}N_2I_2$ requires C, 52·9; H, 4·3; I, 38·7%).

β-Phenyl-γ-2-quinolylbutyric Acid.—Quinaldine (14·3 g.), quinaldine hydrochloride (2 g.), and ethyl cinnamate were heated at 250° during 5 hr. The product was cooled, then treated with an excess of 2N-hydrochloric acid, and unchanged ethyl cinnamate extracted with ether. The aqueous solution was basified with 2N-ammonia, and the resulting reddish-brown oil extracted with ether. After drying of the extract (Na_2SO_4) and removal of the ether an oil was obtained which on distillation at 2 mm. gave fraction (1), quinaldine (10·3 g., b. p. 100°), (2) a viscous red oil (2·82 g., b. p. 190—205°). The latter was refluxed for 3 hr. with alcoholic 10% potassium hydroxide solution (50 ml.), the solvent was distilled off, and the residue treated with a little water. Acidification of the solution with 10% acetic acid yielded a white product which crystallised from aqueous ethanol as colourless leaflets, m. p. 193°.

Ultraviolet Absorption Spectra.—The spectra were determined for 2 : 2 : 4-trimethylpentane solutions with a Unicam S.P. 500 spectrophotometer and 1 cm. quartz cells.

ROYAL TECHNICAL COLLEGE, SALFORD. [*Received, November 18th,* 1958.]

325. *The Component Acids and Glycerides of an Indian Bear Fat.*

By S. P. PATHAK, B. N. TRIVEDI, and S. K. ROY.

The mixed acids from the depot fat of a wild bear (*Ursus torquatus*) were separated by the lead salt–alcohol method and their composition was studied by the ester-fractionation procedure. The fat, in general, is similar in composition to fats of other omnivorous land animals. Low-temperature crystallisation was used for the determination of the glyceride structure; neither the rule of " even " nor that of " random " distribution was followed.

THE common land-animal fats whose fatty acid compositions are available are from sacred baboon, Ceylon sloth bear, lion and cat,[1] bear,[2] puma,[3,4] tiger,[5] badger,[6] camel, deer,[7] elephant, horse, ox, sheep, and pig,[8] mostly domesticated or in captivity. To these we now add that from Indian bear.

TABLE 1. *Component acids and glycerides of fats of omnivorous land animals.*

Acids	Ceylon sloth bear [1]	Sacred baboon [1]	Indian bear [a]
Myristic	2·6	3·2	1·8
Palmitic	28·7	18·9	25·0
Stearic	3·4	11·9	10·7
Tetradecenoic	—	0·8	1·3
Hexadecenoic	10·6	3·8	18·0
Oleic	50·5	53·8	34·5
Linoleic	1·0	13·2	8·7
Linolenic	1·8	—	—
C_{20-22} unsat.	—	0·5	—
Component glyceride groups			
Trisat.	2	—	—
Disaturated-monounsat.	16	10	20·8
Monosat.-diunsat.	68	70	69·3
Triunsat.	14	20	9·9

[a] Present work.

[1] Hilditch, Sime, and Maddison, *Biochem. J.*, 1942, **36**, 98.
[2] Steger and Püschel, *Pharmazie*, 1957, **12**, 821.
[3] Giral, *J.*, 1945, 112.
[4] Gunstone, *Biochem. J.*, 1955, **59**, 455.
[5] Pathak and Agarwal, *J. Sci. Food Agric.*, 1952, **3**, 136.
[6] Gupta, Hilditch, and Meara, *J.*, 1950, 3145.
[7] Gunstone and Paton, *Biochem. J.*, 1953, **54**, 617.
[8] Hilditch, " The Chemical Constitution of Natural Fats," Chapman and Hall, London, 1956.

In general, the pattern of both saturated and unsaturated acids is the same as for the fats of other omnivorous land animals (see Table 1). In detail the bear fat is more saturated—other land-animal fats of Indian origin are more saturated than those of animals from colder climates. The present analysis is also in conformity with the findings of earlier workers.[2]

TABLE 2. *Distribution of acyl groups in the glyceride of bear fat.*

Glycerides	Actual	Computed "Even" [8]	Computed "Random" [10]
Fully saturated	—	—	5·0
Disat.-monounsat.	20·8	11·0	26·0
Monosat.-diunsat.	69·3	89·0	44·0
Triunsat.	9·9	—	25·0

The glyceride structure was determined and is compared in Table 2 with that calculated on the "even" and the "random" pattern of acyl radicals. The present bear fat does not contain any saturated triglycerides (determined by Hilditch and Lea's method [9]), as suggested by the rule of "even" distribution, but in all other respects the composition is intermediate between the two calculated sets of values.

EXPERIMENTAL

A dirty green fat was obtained from the thigh region of a freshly killed female bear (*Ursus torquatus*) from the forest of the Cherpunda area (North India). The saponification equivalent of the purified fat was 283·6 and the iodine value was 62·9 with 1·2% of free fatty acids (as oleic).

Component Acids.—A portion (160 g.) of the fat was saponified and the mixed fatty acids (142·7 g.; I.V. 66·9) were recovered. 98·6 g. of the mixed acids were resolved by the modified

TABLE 3. *Separation of the acids of bear fat by the lead salt–ethanol method.*

Group	Sol. of Pb salt in EtOH at 15°	Weight (g.)	Weight (%)	I val.
X	Insoluble	29·1	29·5	2·8
Y	Soluble	69·5	70·5	91·4

TABLE 4. *Component acids in groups* X *and* Y *from the whole fat of the bear.*

(Figures in parentheses indicate unsaturation, *e.g.*, −2·0 H means monoethenoid).

Acids	Component acids * of groups (%)		Total (%)	Fatty acids in the whole fat exclg. non-sap.	
Saturated	X	Y		% (w/w)	% (mol.)
Myristic	0·9	1·0	1·9	1·8	2·2
Palmitic	20·5	4·4	24·9	25·0	26·2
Stearic	6·8	3·8	10·6	10·7	10·0
Unsaturated					
C_{14}	—	1·3 (−2·0 H)	1·3 (−2·0 H)	1·3	1·5
C_{16}	0·5 (−2·0 H)	17·5 (−2·0 H)	18·0 (−2·0 H)	18·0	19·0
C_{18}	0·7 (−2·0 H)	42·5 (−2·4 H)	43·2 (−2·4 H)	43·2	41·1
Unsap.	0·05	0·06	0·1	—	—

* The figures are derived from quantities of fractions actually obtained on fractionation. Loss was small and ignored. Hence the figures total 100.

Twitchell lead salt method [8] into two groups X and Y (Table 3), which were separately converted into the methyl esters and fractionated in an efficient electrically heated column [11] at about 0·1 mm. The saponification equivalent and iodine value of each fraction were determined. The composition of the fat, calculated by Hilditch's method,[8] is recorded in Table 4.

Component Glycerides.—Neutral fat was crystallised from acetone and ether at various

[9] Hilditch and Lea, *J.*, 1927, 3106.
[10] Longenecker, *Chem. Rev.*, 1941, **29**, 201.
[11] Longenecker, *J. Soc. Chem. Ind.*, 1937, **56**, 199T.

temperatures as shown in the chart. Fractions of nearly similar iodine values were combined, giving the fractions A, B, and C.

The mixed acids recovered from each fraction A, B, and C were resolved into solid and liquid groups by the usual lead salt–alcohol method.[9] The resolved fractions are designated AA, AB, BA, BB, CA, and CB in Table 5. Each fraction was converted into its methyl ester and then fractionated for the determination of component acids above through the same column. The compositions of the fractions thus obtained were calculated and therefrom those of the major fractions A, B, and C, and finally of the whole fat were obtained (see Table 6).

TABLE 5. *Separation of the mixed acids of glyceride fractions* A, B, *and* C.

		Weight		
Fraction A	Sol. of Pb salt in EtOH at 15°	(g.)	(%)	I val.
AA	Insoluble	22·0	50·7	1·6
AB	Soluble	21·4	49·3	66·6
Fraction B				
BA	Insoluble	21·4	31·2	5·2
BB	Soluble	47·1	68·8	75·7
Fraction C				
CA	Insoluble	33·5	23·0	9·6
CB	Soluble	112·0	77·0	84·5

TABLE 6. *Component acids of glyceride fractions,* A, B, *and* C (mol. %).

Acids	A	B	C	Total
Myristic	0·2	0·5	1·0	1·7
Palmitic	8·0	7·4	9·3	24·7
Stearic	3·1	2·5	5·0	10·6
Tetradecenoic	0·2	0·3	1·1	1·6
Hexadecenoic	1·5	2·9	12·2	16·6
Oleic	5·6	10·3	23·2	39·1
Linoleic	—	1·7	4·0	5·7

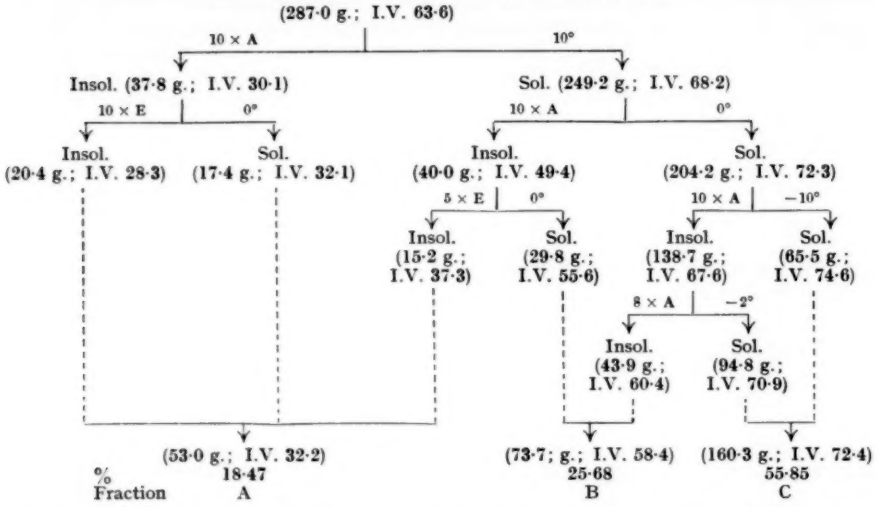
TABLE 7. *Component glycerides (mol. %) of bear fat.*

(Calc. according to the suggestions of Hilditch and Meara, *J. Soc. Chem. Ind.*, 1942, **61**, 117.)

	A	B	C	Whole fat
Component acid groups				
Myristic and " palmitic "	8·2	7·9	10·3	26
Stearic	3·1	2·5	5·0	11
Tetra- and hexa-decenoic	1·7	3·2	13·3	18
" Oleic " and linoleic	5·6	12·0	27·2	45
Component glyceride groups (mol. %)				
Disat.-monounsat.	15·2	5·6	—	21
Monosat.-diunsat.	3·4	20·0	45·9	69
Triunsat.	—	—	9·9	10
" Dipalmito " monoethers	6·0	—	—	6
" Monopalmito " diethers	12·6	23·8	30·9	67
Triethers	—	1·8	24·9	27
" Dioleo " monoethers	3·4	10·4	25·7	40
" Mono-oleo " diethers	10·1	15·2	30·1	55
Triethers	5·1	—	—	5
Possible component glycerides (mol. %)				
Disaturated monounsaturated (20·8%)				
" Dipalmito-olein "	6·0	—	—	6
" Palmito-stearo-olein "	4·1	5·6	—	10
" Palmito "-stearo-hexadecenin	5·1	—	—	5
Monosaturated diunsaturated (69·3%)				
" Palmito-diolein "	3·4	10·4	15·9	29
" Palmito "-hexadeceno-" olein "	—	7·8	15·0	23
Stearo-hexadeceno-" olein "	—	1·8	15·0	17
Triunsaturated (9·9%)				
Hexadeceno-" diolein "	—	—	9·9	10

XUM

Crystallisation of the bear fat, with iodine values of the fractions and sub-fractions (A = *acetone*, E = *ether*, *ml. of solvent/g. of fat*).



The possible component glycerides were calculated from the composition of the individual groups of acids by Hilditch's computational method [8] and are given in Table 7.

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DEPARTMENT OF CHEMICAL ENGINEERING AND CHEMICAL TECHNOLOGY,
BANARAS HINDU UNIVERSITY, BANARAS-5, INDIA. [*Received, November 24th*, 1958.]

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326. *Purines, Pyrimidines, and Glyoxalines. Part XIII.* Some New Unambiguous Syntheses of 5-Aminoglyoxalines and 5-Aminoglyoxaline-4-carboxyamides, and a Synthesis of 5-Amino-1-β-D-ribofuranosylglyoxaline-4-carboxyamide.*

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Ethyl *N*-cyanomethyl-acetimidate (or -formimidate) prepared from ethyl acetimidate (or formimidate) hydrochloride and aminoacetonitrile, with primary amines including D-galactosylamine, gave corresponding 1-substituted 5-aminoglyoxalines. The related ethyl *N*-(carbamoylcyanomethyl)-acetimidate (or -formimidate) and ethyl *N*-(cyano-*N*-methylcarbamoylmethyl)-acetimidate (or -formimidate) were prepared from α-amino-α-cyanoacetamide or α-amino-α-cyano-*N*-methylacetamide and ethyl acetimidate (or formimidate) hydrochloride in aqueous solution. Reaction of these compounds with primary amines readily gave 1-substituted 5-aminoglyoxaline-4-carboxyamides (or -*N*-methylcarboxyamides). The reactions have been adapted to include a synthesis of 5-amino-1-β-D-ribofuranosylglyoxaline-4-carboxyamide.

INTERMEDIATES in the biosynthesis of purine nucleotides include the 5′-*O*-phosphates of 5-amino-1-β-D-ribofuranosylglyoxaline (Ia; R = H, R′ = β-D-ribofuranosyl) and the corresponding 4-carboxyamide (Ib; R = R″ = H, R′ = β-D-ribofuranosyl).[1]

* Part XII, *J.*, 1959, 1169.

[1] Buchanan, "Chemistry and Biology of the Purines," Ciba Foundation Symposium, Little, Brown & Co., Boston, 1957; Baddiley and Buchanan, *Quart. Rev.*, 1957, 329.

The unstable parent aminoglyoxaline (Ia; R = R′ = H) has been prepared as a hydrochloride by reduction of 5-nitroglyoxaline [2] (IIa; R = H), and a 1-methyl derivative (Ia; R = H, R′ = Me) was obtained by desulphurisation of the mercaptoglyoxaline (Ia; R = SH, R′ = Me) with Raney nickel.[3] The last compound was prepared by reaction of methyl *iso*thiocyanate with aminoacetonitrile and base-catalysed rearrangement of the resulting thiazole (IIIa).

The parent carboxyamide (Ib; R = R′ = R″ = H) has been prepared by (1) the cyclisation of α-*N*-formamidomalonamidamidine,[4] (2) reaction of formamidine hydrochloride [5] or ethyl formimidate [6] with α-amino-α-cyanoacetamide (other imidates give 2-substituted derivatives [7]), and (3) reduction of 5-nitroglyoxaline-4-carboxyamide [8] (IIc; R = H). In addition, the amidine (Id; R = R′ = H) has been obtained by cyclisation of α-*N*-formamidomalondiamidine [9] or by acid hydrolysis of adenine,[10] the ester (Ic; R = R′ = H) from formamidine hydrochloride and ethyl α-amino-α-cyanoacetate,[11] and a 1-methyl derivative (Ib; R = R″ = H, R′ = Me) by desulphurisation of the mercaptoglyoxaline (Ib; R = SH, R′ = Me, R″ = H) with Raney nickel.[3] The last compound was prepared from methyl *iso*thiocyanate and ethyl α-amino-α-cyanoacetate which gave the thiazole (IIIb) from which the amide (IIIc) was obtained, and this rearranged to the thiol (Ib; R = SH, R′ = Me, R″ = H) with alkali.

Method (3) has been adapted to a synthesis of the riboside (Ib; R = R″ = H, R′ = β-D-ribofuranosyl) by reaction of 2 : 3 : 5-tri-*O*-benzoylribofuranosyl chloride with the nitroglyoxaline (IIb; R = H) to give a mixture of the isomeric 1- and 3-substituted derivatives which were separated; the 1-isomer (IIb; R = β-D-2 : 3 : 5-tri-*O*-benzoylribofuranosyl) with ammonia gave the amide (IIc; R = β-D-ribofuranosyl) which was reduced to the amino-carboxyamide (Ib; R = R″ = H, R′ = β-D-ribofuranosyl).[12] In a second synthesis benzylation of inosine gave the 1-benzyl derivative (IV; R = β-D-ribofuranosyl, R′ = CH_2Ph), converted by alkali into the *N*-benzyl-carboxyamide (Ib; R = H, R′ = β-D-ribofuranosyl, R″ = CH_2Ph) which with sodium in liquid ammonia gave the required product (Ib; R = R″ = H, R′ = β-D-ribofuranosyl).[13]

Apart from their biochemical interest, the amino-carboxyamides (Ib) and related esters, amidines, etc., are of potential value as intermediates for the synthesis of purines and purine nucleosides and nucleotides. The parent amide (Ib; R = R′ = H) and the corresponding ethyl ester and amidine have been converted into several purines by closure of the pyrimidine ring with formic acid and its derivatives, urea, and *iso*cyanates, and 2-azapurines are obtained with nitrous acid.[14] In addition, the riboside (Ib; R = R″ = H, R′ = β-D-ribofuranosyl) has similarly been converted into inosine with formic acid and acetic anhydride.[15,9]

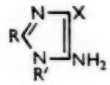
We now report some preliminary experiments which lead to simple, convenient, and unambiguous syntheses of compounds of type (Ib) by methods which closely parallel previous syntheses of pyrimidines and pyrimidine nucleosides, in that a 1-substituent is introduced *via* a primary amine. The preparation of glyoxalines (Ia) and (Ib) through the thiazoles (IIIa) and (IIIc) is also unambiguous but has not been extended to include

[2] Hunter and Nelson, *Canad. J. Res.*, 1941, **19**, *B*, 296.
[3] Cook, Downer, and Heilbron, *J.*, 1948, 2028.
[4] Shaw and Woolley, *J. Biol. Chem.*, 1949, **181**, 89.
[5] Cook, Heilbron, and Smith, *J.*, 1949, 1440.
[6] Miller, Gurin, and Wilson, *Science*, 1950, **112**, 654.
[7] *Idem*, *J. Amer. Chem. Soc.*, 1952, **74**, 2892.
[8] Windaus and Langenbeck, *Ber.*, 1923, **56**, 683.
[9] Shaw, *J. Biol. Chem.*, 1950, **185**, 439.
[10] Cavalieri, Tinker, and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 3973.
[11] Cook and Heilbron, B.P. 683,523/1952.
[12] Baddiley, Buchanan, and Stewart, *Proc. Chem. Soc.*, 1957, 149.
[13] Shaw, *J. Amer. Chem. Soc.*, 1958, **80**, 3899.
[14] Hofmann, "Imidazoles and Derivatives," Interscience Publ. Inc., New York, 1953; Chargaff and Davidson, "The Nucleic Acids," Academic Press, Inc., New York, 1955.
[15] Greenberg and Spilman, *J. Biol. Chem.*, 1956, **219**, 411.

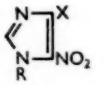
the preparation of glycosides although the use of glycosyl *iso*thiocyanates in these reactions was foreshadowed.[16]

Initially we examined the compound (V) which has been prepared from ethyl acetimidate hydrochloride and glycine ethyl ester.[17] This reacted smoothly with methylamine and ethylamine, to give the corresponding hydroxyglyoxalines (VIa; R = Me and Et respectively). The analogous nitrile (VII; R = Me), prepared in a similar manner from ethyl acetimidate hydrochloride and aminoacetonitrile,[18] with methylamine and D-galactosylamine readily gave the aminoglyoxalines (Ia; R = Me, R′ = Me or D-galacto-pyranosyl respectively). The structures assigned to these compounds followed from their ability to diazotise and couple with β-naphthol or α-naphthylethylenediamine, and the absence of the CN bands in their infrared spectra.

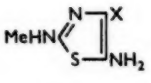
In a similar manner, reaction of aminoacetonitrile and ethyl formimidate hydrochloride in water readily gave the linear compound (VII; R = H) which with methylamine and ethylamine afforded the aminoglyoxalines (Ia; R = H, R′ = Me or Et respectively). An attempt was also made to prepare the riboside (Ia; R = H, R′ = β-D-ribofuranosyl) by reaction of the compound (VII; R = H) with 2 : 3 : 5-tri-*O*-benzoylribofuranosylamine. Debenzoylation of the product gave unstable material, and the riboside could not be isolated although there is little doubt that it was formed during these reactions, since ultraviolet absorption spectra of the solutions were similar to those recorded for the 5′-phosphate.[19]



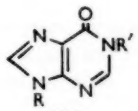
(Ia) X = H
(Ib) X = CO·NHR″
(Ic) X = CO_2Et
(Id) X = C(:NH)·NH_2



(IIa) X = H
(IIb) X = CO_2Me
(IIc) X = CO·NH_2

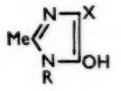


(IIIa) X = H
(IIIb) X = CO_2Et
(IIIc) X = CO·NH_2



(IV)

(V) Me·C(OEt):N·CH_2·CO_2Et
(VII) R·C(OEt):N·CH_2·CN
(VIII) R·C(OEt):N·CH(CN)·CO·NHR′



(VIa) X = H
(VIb) X = CO_2Et

These reactions were extended to include the preparation of aminoglyoxalinecarboxy-amides. When ethyl acetimidate hydrochloride and α-amino-α-cyanoacetamide were mixed in aqueous solution at room temperature, the linear derivative (VIII; R = Me, R′ = H) quickly separated. It reacted rapidly and smoothly with ammonia, methylamine, *cyclo*hexylamine, and D-xylosylamine to give the corresponding amino-amides (Ib; R = Me, R′ = H, Me, *cyclo*hexyl, and D-xylopyranosyl, R″ = H). The structures assigned to these compounds followed from their ability to diazotise and couple, and in addition the 1-methyl derivative (Ib; R = R′ = Me, R″ = H) is apparently identical with the material prepared from the ester (IIIc).

Similarly, the imino-ether (VIII; R = R′ = H) was readily obtained crystalline by extraction of an aqueous solution of α-amino-α-cyanoacetamide and ethyl formimidate hydrochloride with ether. This compound with ammonia, methylamine, ethylamine, and *cyclo*hexylamine gave the glyoxalines (Ib; R = R″ = H, R′ = H, Me, Et, or *cyclo*-hexyl). When exposed to the atmosphere the imidate slowly decomposed to a higher-melting more stable compound, presumably the glyoxaline [Ib; R = R″ = H, R′ = ·CH(CN)·CO·NH_2], which is probably formed by partial hydrolysis of the linear derivative

[16] Heilbron, *J.*, 1949, 2099.
[17] Schmidt, *Ber.*, 1914, **47**, 2548; Cornforth and Cornforth, *J.*, 1947, 96.
[18] Cornforth, *J.*, 1948, 1969.
[19] Levenberg and Buchanan, *J. Biol. Chem.*, 1957, **224**, 1005.

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(VIII; R = R′ = H) and subsequent condensation of the α-amino-α-cyanoacetamide so formed with the imidate (VIII; R = R′ = H). A similar reaction has been observed by Cornforth and Cornforth [17] in which ethyl *N*-(diethoxycarbonylmethyl)acetimidate is converted into the glyoxaline [VIb; R = $CH(CO_2Et)_2$].

Also, reaction of the imino-ether (VIII; R = R′ = H) with 2 : 3 : 5-tri-*O*-benzoyl-ribofuranosylamine and debenzoylation of the product gave the riboside (Ib; R = R″ = H, R′ = β-D-ribofuranosyl) as an analytically pure glass; it readily gave a pure crystalline picrate, however, and its paper-chromatographic behaviour in several solvent systems, and its ultraviolet absorption spectra at differing pH values, were identical with those reported for the naturally occurring material.[15] In addition, the structure of the riboside was confirmed by conversion into inosine (IV; R = β-D-ribofuranosyl, R′ = H). The average yield of glyoxaline riboside obtained was about 40%.

These reactions clearly allow many variations. One of these in which we have been interested includes the preparation of *N*-substituted carboxyamides (Ib; R″ = alkyl, aryl, etc.) in which the substituent R″ would eventually appear, after cyclisation, at position 1 in the corresponding purine. Accordingly, in order to establish the generality of the reactions, we have examined the preparation of the group of compounds (Ib; R″ = Me). α-Cyano-*N*-methylacetamide with nitrous acid gave the *C*-hydroxyimino-derivative which was readily reduced by aluminium amalgam in aqueous methanol to α-amino-α-cyano-*N*-methylacetamide. This with ethyl acetimidate (or formimidate) hydrochloride in water gave the linear imidates (VIII; R = R′ = Me; and R = H, R′ = Me) from which the glyoxalines (Ib; R = R″ = Me, R′ = H, Me, or *cyclo*hexyl) and (Ib; R = H, R′ = H or Me, R″ = Me) were obtained by reaction with ammonia or the appropriate primary amines.

Experimental

5-Hydroxy-1 : 2-dimethylglyoxaline.—To a solution of ethyl *N*-(ethoxycarbonylmethyl)-acetimidate [17] (3·18 g.) in ethanol (2 ml.) was added 33% ethanolic methylamine (6 ml.). The mixture was set aside for 24 hr., then a crystalline precipitate was collected. The *glyoxaline* (0·95 g.) separated from ethyl acetate as needles, m. p. 165° (decomp.) (Found: C, 53·1; H, 6·95; N, 24·55. $C_5H_8ON_2$ requires C, 53·55; H, 7·2; N, 25·0%). The compound gave a blue colour with ferric chloride.

1-Ethyl-5-hydroxy-2-methylglyoxaline.—Ethyl *N*-(ethoxycarbonylmethyl)acetimidate (10 g.) and ethylamine (5 ml.) similarly gave the *glyoxaline* (9·7 g.) which separated from ethyl acetate as needles, m. p. 190° (decomp.) (Found: C, 57·1; H, 8·1; N, 21·9. $C_6H_{10}ON_2$ requires C, 57·1; H, 7·95; N, 22·2%).

5-Amino-1 : 2-dimethylglyoxaline.—33% Ethanolic methylamine (3 ml.) was added to ethyl *N*-cyanomethylacetimidate [18] (4·5 g.) in ethanol (10 ml.). After 20 min. the solution was treated with picric acid (7 g.) in ethanol. The *glyoxaline picrate* was filtered off after 12 hr. It separated from water as brownish-yellow needles, m. p. 193° (decomp.) (Found: C, 39·05; H, 3·8; N, 24·55. $C_5H_9N_3,C_6H_3O_7N_3$ requires C, 38·85; H, 3·55; N, 24·7%).

5-Amino-1-D-galactosyl-2-methylglyoxaline.—A suspension of D-galactosylamine (10·4 g.) in ethanol (30 ml.) was shaken with ethyl *N*-cyanomethylacetimidate (7·3 g.) for 20 min. with gentle warming. The mixture was filtered from undissolved galactosylamine (8 g.), and picric acid (2 g.) in ethanol added to the filtrate. The *glyoxaline picrate* (0·6 g.) separated after 24 hr. and recrystallised from water as brownish-yellow plates, m. p. 172° (decomp.) (Found: C, 39·7; H, 4·35; N, 26·3. $C_{10}H_{17}O_5N_3,C_6H_3O_7N_3$ requires C, 39·35; H, 4·1; N, 26·3%).

Ethyl N-Cyanomethylformimidate.—A solution of potassium carbonate (6·9 g.) and amino-acetonitrile sulphate (7·7 g.) in water (20 ml.) was covered with ether (200 ml.), then treated with ethyl formimidate hydrochloride (5·5 g.). The mixture was shaken for 3 min., the ether decanted, and the mixture shaken with a further portion of ether (100 ml.). The combined and dried extracts were evaporated to an oil which was distilled *in vacuo* to give *ethyl N-cyano-methylformimidate* (1·96 g.), b. p. 51°/0·8 mm., n_D^{29} 1·4305 (Found: C, 53·4; H, 7·3; N, 24·8. $C_5H_8ON_2$ requires C, 53·55; H, 7·2; N, 25·0%). The compound slowly darkened at room temperature but was stable for long periods when kept in the refrigerator.

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5-Amino-1-methylglyoxaline.—The foregoing imidate (0·17 g.) in methanol (1 ml.) was heated on a water-bath for 5 min. with 33% ethanolic methylamine (0·17 ml.). Saturated methanolic picric acid was added to the cooled solution to precipitate the glyoxaline picrate (0·2 g.), greenish-yellow prisms, m. p. 189° (decomp.) (from ethanol) (Found: C, 36·65; H, 2·9; N, 25·6. Calc. for $C_4H_7N_3,C_6H_3O_7N_3$: C, 36·8; H, 3·1; N, 25·8%). Cook, Downer, and Heilbron [3] describe the free base as very unstable and give m. p. 177° (decomp.) for the picrate.

5-Amino-1-ethylglyoxaline.—Similarly the imidate (0·34 g.) and 33% ethanolic ethylamine (0·5 ml.) gave the *glyoxaline picrate* (0·31 g.), pale yellow laths, m. p. 185° (decomp.) (from ethanol) (Found: C, 38·9; H, 3·4; N, 24·4. $C_5H_9N_3,C_6H_3O_7N_3$ requires C, 38·8; H, 3·6; N, 24·7%).

Ethyl N-(Carbamoylcyanomethyl)acetimidate.—Water (10 ml.) was added to a mixture of α-amino-α-cyanoacetamide [20] (5 g.) and ethyl acetimidate hydrochloride (12 g.). The mixture was shaken for a few min., a clear solution being obtained which then rapidly gave a crystalline precipitate. The *acetimidate* (5·7 g.) separated from ethyl acetate–light petroleum (b. p. 40—60°) as plates, m. p. 105° (Found: C, 49·95; H, 6·5; N, 24·8. $C_7H_{11}O_2N_3$ requires C, 49·7; H, 6·55; N, 24·85%).

5-Amino-1 : 2-dimethylglyoxaline-4-carboxyamide.—The foregoing acetimidate (0·4 g.) in methanol (1 ml.) with 33% ethanolic methylamine (0·3 ml.) gave after a short time a crystalline precipitate. The *glyoxaline* (0·13 g.) separated from methanol as plates, m. p. 286° (decomp.) (Found: C, 46·95; H, 6·7; N, 36·3. $C_6H_{10}ON_4$ requires C, 46·75; H, 6·55; N, 36·4%). A further quantity (0·07 g.) of the glyoxaline separated from the mother-liquors after 1 hr. The glyoxaline gave red colours with diazotised sulphanilic acid or when diazotised and coupled with alkaline β-naphthol.

5-Amino-1-cyclohexyl-2-methylglyoxaline-4-carboxyamide.—The foregoing acetimidate (1 g.) and *cyclo*hexylamine (0·7 ml.) were heated in methanol (1·5 ml.) for 15 min. on a water-bath. The cooled solution gave a crystalline precipitate of the *glyoxaline monohydrate* (0·35 g.), needles (from ethanol), m. p. 240° (decomp.) (Found: C, 54·8; H, 8·15; N, 23·2. $C_{11}H_{18}ON_4,H_2O$ requires C, 55·0; H, 8·35; N, 23·35%). A further quantity (0·25 g.) of the glyoxaline separated from the mother-liquors after evaporation.

5-Amino-2-methylglyoxaline-4-carboxyamide.—The acetimidate (0·5 g.) was heated on a water-bath for 20 min. with 10% ethanolic ammonia (5 ml.). Excess of ammonia was removed by evaporation and the solution treated with picric acid (0·7 g.) in ethanol (10 ml.) to give the *glyoxaline picrate* (0·8 g.), prisms (from ethanol), m. p. 240° (decomp. with darkening from 200°) (Found: C, 36·05; H, 2·95; N, 24·25. $C_5H_8ON_4,C_6H_3O_7N_3$ requires C, 35·8; H, 3·0; N, 24·65%). A suspension of the picrate (0·5 g.) in acetone with dry hydrogen chloride gave a colourless insoluble precipitate. The glyoxaline hydrochloride (0·1 g.) separated from methanol–ether as prisms, m. p. 246—247° (with preliminary darkening) (Found: C, 34·15; H, 4·9; N, 31·55. Calc. for $C_5H_8ON_4,HCl$: C, 34·0; H, 5·15; N, 31·75%). Cook *et al.*[3] give m. p. 239—240°.

5-Amino-2-methyl-1-D-xylopyranosylglyoxaline-4-carboxyamide.—A suspension of D-xylosylamine (0·8 g.) in ethanol (15 ml.) containing the above acetimidate (0·7 g.) was gently warmed and stirred until the xylosylamine had dissolved (20 min.). The solution was heated for a further 15 min., cooled, and set aside overnight, a crystalline precipitate separating. The *glyoxaline monohydrate* (0·26 g.) crystallised from water as needles, m. p. 186—187° (decomp.) (Found: C, 41·45; H, 6·05; N, 19·45. $C_{10}H_{16}O_5N_4,H_2O$ requires C, 41·4; H, 6·25; N, 19·45%). The compound gave a red colour with diazotised sulphanilic acid, and diazotised and coupled with alkaline β-naphthol to give a red colour.

9-cyclohexyl-8-methylhypoxanthine.—A solution of 5-amino-1-*cyclo*hexyl-2-methylglyoxaline-4-carboxyamide (0·33 g.) in acetic anhydride (5 ml.) and formic acid (5 ml.) was heated on a water-bath for 2 hr. The solution was evaporated to dryness *in vacuo* and the residue evaporated with ethanol to give a solid. The *hypoxanthine* (0·3 g.) separated from ethanol as short rods, m. p. 285° (Found: C, 61·6; H, 7·15; N, 24·05. $C_{12}H_{16}ON_4$ requires C, 62·05; H, 6·95; N, 24·15%).

Ethyl N-(Carbamoylcyanomethyl)formimidate.—A solution of α-amino-α-cyanoacetamide (2 g.) in water (40 ml.), covered by ether (200 ml.), was treated with ethyl formimidate hydrochloride (2·5 g.), and the mixture was shaken. The ethereal solution was separated, and the aqueous phase treated with a further portion of the imidate (1 g.) and again extracted with ether (100 ml.). The combined, dried extracts were evaporated *in vacuo* to about 10 ml.,

[20] Smith and Yates, *J. Amer. Chem. Soc.*, 1954, **76**, 6080.

crystals separating. The *formimidate* (0·625 g.) was pure at this stage but crystallised from ether as needles, m. p. 86—87° (Found: C, 46·5; H, 5·7; N, 27·3. $C_6H_9O_2N_3$ requires C, 46·4; H, 5·8; N, 27·1%). A further quantity (0·315 g.) was obtained from the mother-liquors. In this preparation the ethereal solution should not be evaporated to dryness, and the compound should be kept in a desiccator. When exposed to the atmosphere the compound slowly decomposed into a more stable substance. This, presumably *5-amino-2-(carbamoylcyanomethyl)glyoxaline-4-carboxyamide*, separated from water as needles, m. p. 212—216° (decomp.) (Found: C, 40·3; H, 3·4; N, 40·0. $C_7H_8O_2N_6$ requires C, 40·4; H, 3·9; N, 40·4%).

5-Aminoglyoxaline-4-carboxyamide.—The foregoing formimidate (0·1 g.) in methanol (1 ml.) was warmed with methanolic ammonia for 5 min. Evaporation then gave the glyoxaline (0·05 g.) which separated from ethanol as needles, m. p. 170° (Found: C, 37·95; H, 4·7; N, 44·35. Calc. for $C_4H_6ON_4$: C, 38·1; H, 4·8; N, 44·45%). The mother-liquors with picric acid gave the glyoxaline picrate which separated from acetic acid, as an *adduct* with acetic acid, as greenish-yellow prisms, m. p. 230° (decomp.) (Found: C, 34·9; H, 2·9; N, 23·45. $C_4H_6ON_4,C_2H_4O_2,C_6H_3O_7N_3$ requires C, 34·7; H, 3·2; N, 23·6%), or from ethanol as yellow prisms, m. p. 240° (decomp.) (Found: C, 33·65; H, 2·4; N, 27·55. Calc. for $C_4H_6ON_4,C_6H_3O_7N_3$: C, 33·8; H, 2·55; N, 27·6%).

5-Amino-1-methylglyoxaline-4-carboxyamide.—The foregoing formimidate (0·2 g.) in methanol (1 ml.) was heated on a water-bath for 5 min. with 33% methanolic methylamine (0·2 ml.). The cooled solution gave a crystalline precipitate. The glyoxaline (0·11 g.) separated from ethanol as needles, m. p. 260° (Found: C, 42·85; H, 5·5; N, 40·0. Calc. for $C_5H_8ON_4$: C, 42·85; H, 5·75; N, 40·0%). Cook, Downer, and Heilbron [3] give m. p. 254°. The compound gave a red colour with diazotised sulphanilic acid, and after treatment with nitrous acid followed by alkaline β-naphthol. The mother-liquor from this experiment with methanolic picric acid gave the *glyoxaline picrate* (0·1 g.), greenish-brown prisms (from acetic acid), m. p. 249° (decomp.) (Found: C, 35·9; H, 3·0; N, 26·5. $C_5H_8ON_4,C_6H_3O_7N_3$ requires C, 35·8; H, 3·0; N, 26·6%).

5-Amino-1-ethylglyoxaline-4-carboxyamide.—The foregoing formimidate (0·25 g.) in methanol (1 ml.) with 33% ethanolic ethylamine (0·3 ml.) precipitated the *glyoxaline* (0·15 g.), needles (from ethanol), m. p. 230—232° (Found: C, 46·7; H, 6·3; N, 36·6. $C_6H_{10}ON_4$ requires C, 46·7; H, 6·5; N, 36·3%). The mother-liquors gave the *glyoxaline picrate* (0·09 g.), greenish-yellow needles (from acetic acid), m. p. 240° (decomp. with preliminary decomp.) (Found: C, 37·6; H, 3·4; N, 25·6. $C_6H_{10}ON_4,C_6H_3O_7N_3$ requires C, 37·6; H, 3·4; N, 25·6%).

5-Amino-1-cyclohexylglyoxaline-4-carboxyamide.—The above formimidate (0·2 g.) in methanol (2 ml.) and *cyclo*hexylamine (0·13 g.) gave the *glyoxaline* (0·11 g.), needles (from ethanol), m. p. 209° (Found: C, 57·6; H, 7·5; N, 27·0. $C_{10}H_{16}ON_4$ requires C, 57·6; H, 7·7; N, 26·9%).

5-Amino-1-β-D-ribofuranosylglyoxaline-4-carboxyamide.—2 : 3 : 5-Tri-*O*-benzoylribofuranosyl azide [21] (2·44 g.) in ethyl acetate (300 ml.) was hydrogenated over platinic oxide (0·2 g.) for 2 hr. The solution was treated with the foregoing formimidate (0·76 g.) then heated on a water-bath for 30 min. and finally evaporated *in vacuo* to a gum. This was dissolved in chloroform, filtered from a little amorphous material, and again evaporated and the residue in methanol (20 ml.) was treated with a solution from sodium (0·012 g.) in methanol (5 ml.). After 24 hr. the solution was treated with a slight excess of " Zeocarb 225 " to remove sodium, then evaporated *in vacuo*, and the residue extracted with ether and evaporated with water (2 × 25 ml.) *in vacuo* to remove methyl benzoate. A pale amber-coloured gum remained, and did not crystallise. A portion of the gum (0·1 g.) with aqueous picric acid immediately gave the glyoxaline picrate (0·07 g.), m. p. 164° (decomp.), which was pure but crystallised from water (Found: C, 35·45; H, 3·65; N, 19·4. Calc. for $C_9H_{14}O_5N_4,C_6H_3O_7N_3,H_2O$: C, 35·65; H, 3·7; N, 19·4%). A further portion (0·4 g.) of the gum was purified by ion-exchange chromatography using Greenberg and Spilman's method; [15] a sharp fraction with $\lambda_{max.}$ 267 mμ was readily eluted from the column. Evaporation of this fraction gave the glyoxaline as an almost colourless glass (Found: C, 39·35; H, 5·6; N, 20·55. Calc. for $C_9H_{14}O_5N_4,H_2O$: C, 39·15; H, 5·8; N, 20·3%). The substance gave a single absorbing spot on paper chromatograms with R_P values very similar to those reported for the natural material. In addition the ultraviolet absorption spectra of the compound in aqueous solution at different pH values were identical with those recorded.[15] An average yield of the riboside from several experiments was about 40%. The compound was readily converted into inosine by E. Shaw's method [9]

[21] Baddiley, Buchanan, Hodges, and Prescott, *J.*, 1957, 4769.

and was identified by paper chromatography in several solvents, and spectroscopically. Inosine was the sole absorbing material formed in this reaction.

α-Cyano-α-hydroxyimino-N-methylacetamide.—α-Cyano-*N*-methylacetamide (127 g.) and sodium nitrite (92 g.) in water (300 ml.) with acetic acid (120 ml.) gave overnight a crystalline precipitate. This was dissolved in water and acidified with hydrochloric acid to precipitate the *hydroxyimino-derivative* (45 g.) which crystallised from water as needles, m. p. 212° (Found: C, 37·85; H, 3·9; N, 32·95. $C_4H_5O_2N_3$ requires C, 37·8; H, 3·95; N, 33·05%).

α-Amino-α-cyano-N-methylacetamide.—A solution of the foregoing hydroxyimino-compound (45 g.) in methanol (200 ml.) was added slowly to a mixture of aluminium amalgam (from 20 g. of aluminium) and methanol (200 ml.) with stirring during 30 min. Water (24 ml.) was added gradually to the stirred mixture which was kept at 30—40°. When the reaction was complete (2—3 hr.) the mixture was filtered and the solid washed with hot methanol (3 × 50 ml.). Evaporation of the combined methanol solutions gave *α-amino-α-cyano-N-methylacetamide* (7 g.) which crystallised from ethyl acetate as prisms, m. p. 115—116° (Found: C, 42·7; H, 6·15; N, 36·7. $C_4H_7ON_3$ requires C, 42·45; H, 6·25; N, 37·15%). A further quantity (5 g.) of the amine was obtained from the mother liquors.

Ethyl N-(Cyano-N-methylcarbamoylmethyl)acetimidate.—A mixture of ethyl acetimidate hydrochloride (10 g.) and α-amino-α-cyano-*N*-methylacetamide (5 g.) was shaken with water (10 ml.). A clear solution was soon obtained. This was extracted with ether. Evaporation of the dried extract gave an oil which soon solidified. The *acetimidate* (3·7 g.) crystallised from ethyl acetate–light petroleum (b. p. 60—80°) as needles, m. p. 72° (Found: C, 52·05; H, 7·05; N, 23·25. $C_9H_{13}O_3N_3$ requires C, 52·45; H, 7·15; N, 22·95%).

5-Amino-2-methylglyoxaline-4-N-methylcarboxyamide.—The foregoing acetimidate (0·25 g.) in ethanol (1·5 ml.) was heated on a water-bath for 20 min. with 15N-ammonia (0·5 ml.). The cooled solution with methanolic picric acid gave a precipitate of the *glyoxaline picrate* (0·44 g.), yellow needles, from much ethanol, m. p. 250° (decomp.) (Found: C, 37·9; H, 3·45; N, 25·3. $C_6H_{10}ON_4,C_6H_3O_7N_3$ requires C, 37·55; H, 3·4; N, 25·6%).

5-Amino-1 : 2-dimethylglyoxaline-4-N-methylcarboxyamide.—The above acetimidate (0·5 g.) in ethanol (3 ml.) was heated on a water-bath with 33% ethanolic methylamine (0·5 ml.) for 30 min. Evaporation of the solution then gave the *glyoxaline* (0·3 g.) which separated from methanol-ether as needles, m. p. 176° (Found: C, 49·9; H, 6·95; N, 33·05. $C_7H_{12}ON_4$ requires C, 50·0; H, 7·2; N, 33·3%). The glyoxaline and methanolic picric acid gave a *picrate*, yellow needles (from ethanol), m. p. 221° (decomp.) (Found: C, 39·45; H, 3·75; N, 24·0. $C_7H_{12}ON_4,C_6H_3O_7N_3$ requires C, 39·3; H, 3·8; N, 24·35%).

5-Amino-1-cyclohexyl-2-methylglyoxaline-4-N-methylcarboxyamide.—The above acetimidate (1 g.) in ethanol (2 ml.) and *cyclo*hexylamine (0·66 ml.) was heated on a water-bath for 30 min. Evaporation then gave an oil which solidified when evaporated with ether. The *glyoxaline monohydrate* (1·04 g.) crystallised from aqueous ethanol as needles, m. p. 161° (with apparent loss of solvent from 100°) (Found: C, 57·15; H, 8·35; N, 21·9. $C_{12}H_{20}ON_4,H_2O$ requires C, 56·7; H, 8·7; N, 22·05%). The *picrate* crystallised from ethanol as lemon-yellow needles, m. p. 220—228° (decomp.) (Found: C, 46·55; H, 4·8; N, 20·95. $C_{12}H_{20}ON_4,C_6H_3O_7N_3$ requires C, 46·45; H, 5·0; N, 21·05%).

Ethyl N-(Cyano-N-methylcarbamoylmethyl)formimidate.—α-Amino-α-cyano-*N*-methylacetamide (2·26 g.) in water (5 ml.) was covered with ether (30 ml.), and the mixture treated with ethyl formimidate hydrochloride (4 g.) with shaking. The ether was separated and the aqueous phase re-extracted. The combined and dried extract was evaporated *in vacuo* to a colourless oil which did not crystallise but was undoubtedly the *formimidate* (Found: N, 24·35. $C_7H_{11}O_2N_3$ requires N, 24·85%).

5-Aminoglyoxaline-4-N-methylcarboxyamide.—The foregoing formimidate (0·5 g.) was warmed on a water-bath for 20 min. with methanolic ammonia. Excess of ammonia was removed and then methanolic picric acid gave the *glyoxaline picrate* (0·88 g.), yellow prisms (from ethanol), m. p. 217° (decomp.) (Found: C, 35·7; H, 3·6; N, 25·15. $C_5H_8ON_4,C_6H_3O_7N_3$ requires C, 35·6; H, 3·0; N, 26·6%).

5-Amino-1-methylglyoxaline-4-N-methylcarboxyamide.—The last formimidate (0·5 g.) was warmed on a water-bath for 20 min. with 33% ethanolic methylamine (1·5 ml.). Excess of amine was removed and the solution treated with methanolic picric acid to give the *glyoxaline picrate* (0·92 g.), yellow needles (from much ethanol), m. p. 222° (decomp. with darkening from 212°) (Found: C, 37·75; H, 3·35; N, 25·6. $C_6H_{10}ON_4,C_6H_3O_7N_3$ requires C, 37·6; H, 3·4;

N, 25·6%). The picrate (0·69 g.) in warm dry acetone (30 ml.) with dry hydrogen chloride gave a precipitate of the *glyoxaline hydrochloride* (0·24 g.), needles (from ethanol–ether), m. p. 238° (decomp.), which retained a little water (Found: C, 33·05; H, 5·2; N, 30·1. $C_5H_8ON_4,HCl,\frac{1}{4}H_2O$ requires C, 33·15; H, 5·25; N, 30·95%).

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UNIVERSITY OF N.S.W., SYDNEY. [*Received, November 26th*, 1958.]

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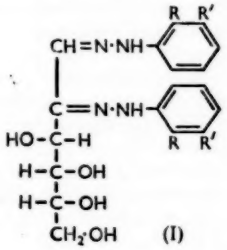
327. *The Scope and Mechanism of Carbohydrate Osotriazole Formation. Part III.*[1] *The Action of Oxidising Agents on* ortho- *and* meta-*Substituted Osazones and Osotriazoles.*

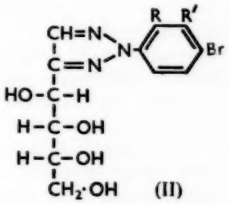
By H. EL KHADEM and ZAKI M. EL-SHAFEI.

Bromine water oxidises *o*- and *m*-tolyl- and *m*-bromophenyl-osazones to osotriazoles and brominates them in the 4-position. Potassium permanganate oxidises the sugar residue and the methyl group in the 3- but not in the 2-position.

IT has been shown[1] that bromine water converts carbohydrate phenylosazones into osotriazoles and brominates them in the 4-position. In the present work, the study was extended to *o*- and *m*-tolyl- and *m*-bromophenyl-osazones and -osotriazoles. Glucose *o*-tolyl-osazone (Ia) and -osotriazole yielded the 4-bromo-2-methylphenylosotriazole (IIa), and the *meta*-isomers yielded the 4-bromo-3-methylphenylosotriazole (IIb). Glucose *m*-bromophenyl-osazone and -osotriazole were likewise brominated in the 4-position, yielding glucose 3 : 4-dibromophenylosotriazole. On similar treatment, glucose *o*-bromophenylosazone gave an osotriazole, m. p. 156°, which is being investigated.



(I)



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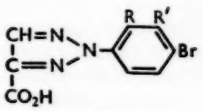

(III)

(a) R = Me, R′ = H

(b) R = H, R′ = Me

To identify the osotriazoles produced, disubstituted osazones were prepared and refluxed with aqueous copper sulphate. The disubstituted osotriazoles were readily obtained except from glucose 2 : 4-dibromophenylosazone which lost one bromine atom and yielded glucose *p*-bromophenylosotriazole.

The action of potassium permanganate on carbohydrate osotriazoles was also studied. This reagent is known[1] to oxidise the sugar residue and methyl group, if present, to carboxylic groups. Thus, glucose *m*-bromophenylosotriazole yielded 2-*m*-bromophenyl-1 : 2 : 3-triazole-4-carboxylic acid, and glucose *m*-tolylosotriazole yielded 2-*m*-carboxyphenyl-1 : 2 : 3-triazole-4-carboxylic acid. In the case of osotriazoles having the methyl group in the *ortho*-position to the triazole ring, potassium permanganate oxidised only the sugar residue: glucose *o*-tolylosotriazole yielded 2-*o*-tolyl-1 : 2 : 3-triazole-4-carboxylic acid, and glucose 4-bromo-2-methylphenylosotriazole (IIa) yielded 2-(4-bromo-2-methylphenyl)-1 : 2 : 3-triazole-4-carboxylic acid (IIIa). This is probably due to the steric

[1] Part II, *J.*, 1958, 3117.

effect of the osotriazole ring. 2-(4-Bromo-2-methylphenyl)-1 : 2 : 3-triazole-4-carboxylic acid (IIIa) was also obtained by the action of bromine water on 2-*o*-tolyl-1 : 2 : 3-triazole-4-carboxylic acid whereas 2-*m*-carboxyphenyl-1 : 2 : 3-triazole-4-carboxylic acid was unaffected by bromine water.

It seems from the above experiments that the controlling factor is the $-I$ effect of the osotriazole ring, initiated from the positive charge on the 2-nitrogen atom. Thus bromination takes place in the 4-position, the least affected by the $-I$ effect, and debromination, as in 2 : 4-dibromophenylosazone, takes place in the 2-position which is the most affected.

The ultraviolet absorption spectra of the above compounds are characterised by a peak between 258 and 276 mμ.

Experimental

Absorption spectra were determined for ethanolic solutions with a Unicam S.P. 500 spectrophotometer. Microanalyses were by A. Bernhardt, Mülheim, W. Germany.

Glucose o-Bromophenylosazone.—Glucose (10 g.) in water (50 ml.) was treated successively with *o*-bromophenylhydrazine hydrochloride (35·5 g.) in water (150 ml.), sodium acetate (35·5 g.) in water (50 ml.), and few drops of acetic acid and heated on the water-bath for 2 hr. The crystalline *osazone* which separated (15 g.) recrystallised from ethanol in needles, m. p. 203—204°, moderately soluble in boiling ethanol and methanol and insoluble in ether and water (Found: C, 41·8, 41·8; H, 3·9, 3·9; N, 10·7, 10·7; Br, 31·0, 31·3. $C_{18}H_{20}O_4N_4Br$ requires C, 41·9; H, 3·9; N, 10·9; Br, 31·0%).

Glucose m-*Bromophenylosazone.*—Glucose (1 g.) in water (50 ml.) was heated with *m*-bromophenylhydrazine (3 g.) and acetic acid (4 ml.) on the water-bath for 40 min. The *osazone* separated (0·8 g.); it recrystallised from ethanol–water in needles, m. p. 204—205° (solubility as above) (Found: C, 42·1; H, 4·0; N, 10·7; Br, 31·4%).

Glucose 4-Bromo-2-methylphenylosazone.—Glucose (10 g.) was treated with 4-bromo-2-methylphenylhydrazine hydrochloride (35 g.) and sodium acetate as before. The *osazone* (15 g.) recrystallised from ethanol in needles, m. p. 184—185° (solubility as above) (Found: C, 44·0; H, 4·7; N, 10·1; Br, 29·3. $C_{20}H_{24}O_4N_4Br_2$ requires C, 44·1; H, 4·4; N, 10·3; Br, 29·4%).

Glucose 4-Bromo-3-methylphenylosazone.—Glucose (10 g.) was treated with 4-bromo-3-methylphenylhydrazine hydrochloride and sodium acetate as before, giving a reddish-brown amorphous precipitate which could not be obtained crystalline. It was filtered off, washed with water, and used as such for the preparation of the osotriazole.

Glucose 2 : 4-Dibromophenylosazone.—Glucose (4 g.) was treated with 2 : 4-dibromophenylhydrazine hydrochloride (19 g.) and sodium acetate as before. The *osazone* (4·5 g.) crystallised from dilute ethanol in needles, m. p. 243—244° (solubility as above) (Found: C, 32·2; H, 2·5; N, 8·3; Br, 47·3. $C_{18}H_{18}O_4N_4Br_4$ requires C, 32·0; H, 2·6; N, 8·3; Br, 47·5%).

Glucose 3 : 4-dibromophenylosazone, similarly prepared, has m. p. 205—206° (Found: C, 31·9; H, 2·9; N, 8·1; Br, 47·0%).

Glucose o-*Tolylosotriazole.*—Glucose *o*-tolylosazone (1·4 g.), suspended in 1% aqueous copper sulphate (100 ml.) and dioxan (20 ml.), was refluxed for 30 min. and filtered. The solution was freed from copper sulphate by passing in hydrogen sulphide and neutralising the mixture with barium carbonate. The filtrate was evaporated to dryness under reduced pressure, and the brown *osotriazole* (0·4 g.) sublimed at 230°/10 mm.; it then crystallised from ethanol in plates, m. p. 126—127°, moderately soluble in hot ethanol and methanol and insoluble in water (Found: C, 55·9; H, 6·3; N, 15·1. $C_{13}H_{17}O_4N_3$ requires C, 55·9; H, 6·1; N, 15·1%).

Glucose m-*tolylosotriazole* crystallised from ethanol in needles, m. p. 194—195°, soluble in hot ethanol and methanol and insoluble in ether and water (Found: C, 55·8; H, 6·1; N, 15·1%).

Glucose m-*Bromophenylosotriazole.*—A solution of glucose *m*-bromophenylosazone (1 g.) in dioxan (20 ml.) was added to a boiling solution of copper sulphate (1 g.) in water (50 ml.) and refluxed for 30 min., then filtered. On concentration, the *osotriazole* separated (0·5 g.) and recrystallised from ethanol in needles, m. p. 209—210° (solubility as above) (Found: C, 41·7; H, 4·2; N, 12·2; Br, 23·2. $C_{12}H_{14}O_4N_3Br$ requires C, 41·9; H, 4·1; N, 12·2; Br, 23·3%).

XUM

Glucose p-*Bromophenylosotriazole*.—Glucose 2 : 4-dibromophenylosazone (2 g.), suspended in a solution of copper sulphate (2 g.) in water (100 ml.) and dioxan (100 ml.), was refluxed for 4 hr. and filtered. To remove dioxan, water (100 ml.) was added, and the solvent distilled off until 200 ml. were collected. The residue was concentrated on the water-bath and the crystals that separated were filtered off (0·5 g.) and recrystallised from ethanol in needles, m. p. 228° alone or mixed with glucose *p*-bromophenylosotriazole (Found: C, 41·6; H, 4·1; N, 12·0; Br, 23·3%).

Glucose 4-*Bromo*-2-*methylphenylosotriazole*.—(*a*) Glucose *o*-tolylosazone (1·6 g.) was treated in the cold with bromine (2 ml.), and the mixture kept overnight. The reddish-brown mass obtained was filtered off (1 g.) and washed with water and ethanol. *Glucose* 4-*bromo*-2-*methylphenylosotriazole* recrystallised from water–ethanol in needles, m. p. 175° (solubility as above) (Found: C, 43·5; H, 4·5; N, 11·4; Br, 22·7. $C_{13}H_{16}O_4N_3Br$ requires C, 43·6; H, 4·5; N, 11·7; Br, 22·3%).

(*b*) Glucose *o*-tolylosotriazole (1·5 g.), similarly treated, gave the same product (1·5 g.), m. p. and mixed m. p. 175° (Found: C, 43·1; H, 4·6; N, 11·4; Br, 22·7%).

(*c*) A suspension of glucose 4-bromo-2-methylphenylosazone (5 g.) in dioxan (70 ml.) and 5% aqueous copper sulphate (100 ml.) was refluxed for 1·5 hr. and filtered hot. Dioxan was removed as before, and the solution concentrated on the water-bath. The osotriazole that separated was filtered off (2 g.) and recrystallised from water–ethanol in needles, m. p. and mixed m. p. 175° (Found: C, 43·4; H, 4·7; N, 11·5; Br, 22·6%).

Glucose 4-*Bromo*-3-*methylphenylosotriazole*.—(*a*) Glucose *m*-tolylosazone (2 g.), suspended in water (100 ml.), was treated in the cold with bromine (3 ml.), and the mixture kept overnight. The mass formed was filtered off and washed with water and ethanol (1 g.). The *osotriazole* recrystallised from ethanol in needles, m. p. 221—222°, soluble in boiling ethanol and methanol and insoluble in acetone and water (Found: C, 43·1; H, 4·4; N, 11·3; Br, 22·0%).

(*b*) Glucose *m*-tolylosotriazole (0·8 g.), treated as in (*a*), gave the same product (0·6 g.), m. p. and mixed m. p. 221—222° (Found: C, 43·1; H, 4·6; N, 11·4; Br, 22·5%).

(*c*) A hot solution of glucose 4-bromo-3-methylphenylosazone (10 g.), in dioxan (100 ml.) was added to a boiling solution of copper sulphate (8 g.) in water (200 ml.), then refluxed for 2 hr. and filtered hot. Dioxan was removed as before, and the solution concentrated on the water-bath. The osotriazole which separated was filtered off (2 g.) and recrystallised from ethanol in needles, m. p. and mixed m. p. 221—222° (Found: C, 43·5; H, 4·7; N, 11·7; Br, 22·5%).

Glucose 3 : 4-*Dibromophenylosotriazole*.—(*a*) Glucose *m*-bromophenylosazone (2 g.), suspended in water (75 ml.), was treated in the cold with bromine (3 ml.) as before. The *osotriazole* was filtered off, washed (1 g.), and recrystallised from ethanol in needles, m. p. 209—210° (solubility as for the preceding compound) (Found: C, 34·1, 34·0; H, 3·1, 3·2; N, 9·8; Br, 38·1. $C_{12}H_{13}O_4N_3Br_2$ requires C, 34·0; H, 3·1; N, 9·9; Br, 37·8%).

(*b*) Glucose *m*-bromophenylosotriazole (2 g.), similarly treated as in (*a*), gave the same product (1·9 g.), m. p. and mixed m. p. 209—210°.

(*c*) Glucose 3 : 4-dibromophenylosazone (2 g.) was treated with copper sulphate as above. The product separated (0·6 g.) and crystallised from ethanol in needles, m. p. and mixed m. p. 209—210° (Found: C, 33·8; H, 3·2; N, 10·0; Br, 37·9%).

2-o-*Tolyl*-1 : 2 : 3-*triazole*-4-*carboxylic Acid*.—A boiling suspension of glucose *o*-tolylosotriazole (0·9 g.) in water (100 ml.) was heated with potassium permanganate (4 g.) for 1·5 hr. The mixture was filtered, treated with sodium hydrogen sulphite, and acidified. The crystals (0·35 g.) recrystallised from water–ethanol in needles, m. p. 146°. 2-o-*Tolyl*-1 : 2 : 3-*triazole*-4-*carboxylic acid* is freely soluble in ethanol and methanol and insoluble in water (Found: C, 59·3; H, 4·4; N, 20·4. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4; N, 20·7%).

2-m-*Carboxyphenyl*-1 : 2 : 3-*triazole*-4-*carboxylic Acid*.—To a boiling suspension of glucose *m*-tolylosotriazole (0·6 g.) in water (100 ml.), potassium permanganate (4 g.) was added, and the mixture treated as above. 2-m-*Carboxyphenyl*-1 : 2 : 3-*triazole*-4-*carboxylic acid* (0·15 g.) crystallised from water–ethanol in needles, m. p. 312° (solubility as for the other acid) (Found: C, 52·0; H, 3·3; N, 18·1. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0; N, 18·0%).

A cold suspension of this acid (0·2 g.) in water (50 ml.) was treated with bromine as before, giving unchanged acid (0·2 g.), m. p. and mixed m. p. 312° (Found: C, 51·7; H, 3·3; N, 18·2%).

2-(4-*Bromo*-2-*methylphenyl*)-1 : 2 : 3-*triazole*-4-*carboxylic Acid*.—(*a*) To a boiling suspension of glucose 4-bromo-2-methylphenylosotriazole (0·9 g.) in water (60 ml.), potassium permanganate (4 g.) was added, and the mixture treated as above. The crystals (0·3 g.) recrystallised from water–ethanol in needles, m. p. 198°. 2-(4-*Bromo*-2-*methylphenyl*)-1 : 2 : 3-*triazole*-4-*carboxylic*

acid is soluble in methanol, ethanol, and chloroform and insoluble in water (Found: C, 42·4; H, 3·0; N, 14·5; Br, 28·5. $C_{10}H_8O_2N_3Br$ requires C, 42·6; H, 2·8; N, 14·9; Br, 28·4%).

(*b*) A cold suspension of 2-*o*-tolyl-1 : 2 : 3-triazole-4-carboxylic acid (0·15 g.) in water (30 ml.) was treated with bromine (1 ml.) and left overnight. The light brown mass obtained was filtered off, washed with water (0·19 g.), and recrystallised from water–ethanol in needles, m. p. and mixed m. p. 198°.

2-m-*Bromophenyl*-1 : 2 : 3-*triazole*-4-*carboxylic Acid*.—Glucose *m*-bromophenylosotriazole (1 g.) in water (150 ml.) was treated with solid potassium permanganate (4 g.) as before. 2-m-*Bromophenyl*-1 : 2 : 3-*triazole*-4-*carboxylic acid* (0·4 g.) recrystallised from water–ethanol in needles, m. p. 197—198° (solubility as in the last case) (Found: C, 40·7; H, 2·6; N, 15·3; Br, 29·6. $C_9H_6O_2N_3Br$ requires C, 40·3; H, 2·2; N, 15·7; Br, 29·9%).

Spectra.—See Table.

Osotriazole (II)					Triazole (cf. III)				
R	R′	*p*-Subst.	$\lambda_{max.}$ (mμ)	log ε	R	R′	*p*-Subst.	$\lambda_{max.}$ (mμ)	log ε
H	Me	H	268	4·07	H	CO_2H	H	272	4·42
H	Br	H	270	4·25	Me	H	Br	258—262	4·06
Me	H	Br	260	4·30	H	Br	H	270	4·19
H	Me	Br	274—276	4·49					
H	Br	Br	274—276	4·54					

The authors thank Professors G. Soliman and Y. Iskander for valuable discussions and Professor E. El Shishiny for making available special apparatus.

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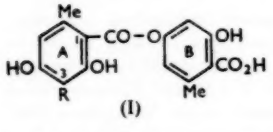
328. *A New Synthesis of Diploschistesic Acid.*

By T. R. SESHADRI and G. B. VENKATASUBRAMANIAN.

Experimental support is provided for the biogenetic view that diploschistesic acid arises from lecanoric acid, by a Gattermann reaction of the latter which gives the 3-aldehyde whence Dakin oxidation affords diploschistesic acid.

DIPLOSCHISTESIC ACID (I; R = OH) occurs in the lichens *Diploschistes scruposus* and *D. bryophilus* alongside lecanoric acid (I; R = H).[1] Its constitution, 3-hydroxylecanoric acid, was suggested by Koller and Hamburg [1] as a result of methanolysis and was confirmed by Asahina and Yasue [2] by a synthesis involving a large number of steps.

Diploschistesic acid is the only case in which the C_8 orsellinic unit of part A has an extra 3-hydroxyl group. Several cases are known where the orsellinic unit B has the extra hydroxyl group in the 3′-position and there *meta*-depsides result.



(I)

The biogenesis of these depsides with extra hydroxyl groups has already been discussed.[3] There are two ways by which they can result: (i) by oxidation at the C_8 stage to yield a 3-hydroxyorsellinic acid derivative [4] with subsequent formation of the depside, and (ii) by oxidation after depside formation. In the first case a *meta*-depside should always be formed owing to its greater stability. The ramalinolic acid series could have arisen by such a method.[5] The formation of diploschistesic acid would support the existence of the second mechanism also. This is supported by the co-occurrence of lecanoric acid and diploschistesic acid in the same lichen.[1]

[1] Koller and Hamburg, *Monatsh.*, 1936, **65**, 367.
[2] Asahina and Yasue, *Ber.*, 1936, **69**, 2327.
[3] Seshadri, *Proc. Indian Acad. Sci.*, 1944, **20**, *A*, 1.
[4] Aghoramurthy and Seshadri, *Proc. Indian Acad. Sci.*, 1952, **35**, *A*, 327.
[5] Asahina and Kusaka, *Ber.*, 1936, **69**, 1896.

The above conclusion has now been verified by the application of *ortho*-nuclear oxidation to lecanoric acid, formation of an aldehyde and subsequent conversion of the aldehyde group into a hydroxyl group. A 3-aldehyde group has now been introduced into lecanoric acid by Gattermann reaction in presence of 2 mols. of aluminium chloride, giving a product shown to have formula (I; R = CHO) by hydrolysis by alkali or acetic acid to atranol and orcinol, and by methanolysis to methyl hæmatommate and orcinol. When a large excess of aluminium chloride was used the depside seemed to undergo preliminary fission followed by a Gattermann reaction, because hæmatommic acid was obtained as the sole product. Dakin oxidation of the 3-formyl-lecanoric acid gave diploschistesic acid (I; R = OH) agreeing in properties with those described by Asahina and Yasue.[2]

Experimental

3-Formyl-lecanoric acid (I; R = CHO).—To an ice-cold solution of dry lecanoric acid (6·4 g.) in absolute ether (150 c.c.) containing zinc cyanide (4·8 g.), a solution of anhydrous aluminium chloride (8 g.) in ether (50 c.c.) was gradually added at 0°, and dry hydrogen chloride passed into the mixture for 3 hr. The cyanide slowly dissolved and a semisolid mass separated. After 24 hr. the ether layer was decanted and the residue treated with crushed ice and later heated for ½ hr. at 80°. The solid product was filtered off and several crystallisations from aqueous dioxan yielded *3-formyl-lecanoric acid* as colourless needles (5 g.), m. p. 174° (decomp.) (Found: C, 58·4; H, 4·4. $C_{17}H_{14}O_8$ requires C, 58·9; H, 4·1%). It readily gave a yellow solution in aqueous sodium hydrogen carbonate, gave a wine-red colour with alcoholic ferric chloride, and readily formed a 2 : 4-dinitrophenylhydrazone.

If, in the above experiment, a large excess of aluminium chloride was employed, the product was hæmatommic acid, m. p. 174°, depressed on admixture with 3-formyl-lecanoric acid. Esterification of the product with methyl sulphate–sodium hydrogen carbonate in acetone gave methyl hæmatommate, m. p. and mixed m. p. 146°. Decarboxylation of hæmatommic acid by boiling with water for 2 hr. gave atranol, m. p. and mixed m. p. 125°.

Fission of 3-Formyl-lecanoric Acid.—(a) *With alkali.* The acid (5 g.) was heated in 10% aqueous sodium hydroxide (100 c.c.) on a water-bath for ½ hr. under nitrogen. Acidification with dilute hydrochloric acid gave atranol, m. p. 125°. The mother-liquor was concentrated under reduced pressure and repeatedly extracted with ether. The ether solution was dried (Na_2SO_4) and the solvent distilled off. The residue, crystallised from chloroform, had m. p. 108° alone or mixed with authentic orcinol.

(b) *Fission with acetic acid.* The aldehydo-acid (5 g.) in 90% acetic acid (100 c.c.) was refluxed for 3 hr. Acetic acid was removed under diminished pressure, and water (20 c.c.) added. The whole was shaken and filtered. The residue (2 g.) was atranol, m. p. 125°. The filtrate on evaporation to dryness gave orcinol, m. p. 107°.

(c) *Methanolysis.* The aldehydo-acid (2 g.) in absolute methanol (200 c.c.) containing a trace of sodium hydroxide (20 mg.) was refluxed for 5 hr. Methanol was removed under diminished pressure and water (50 c.c.) added. The solid that separated crystallised from ethanol, giving methyl hæmatommate, m. p. 146°. The filtrate on evaporation to dryness yielded orcinol, m. p. 107°.

Diploschistesic Acid (I; R = OH).—The aldehydo-acid (1 g.) in 4% aqueous sodium hydroxide (6 c.c.) was cooled to 10°. A 6% solution (2·5 c.c.) of hydrogen peroxide was added and the mixture shaken for 1 hr. The solid that separated on acidification with dilute hydrochloric acid was repeatedly crystallised from aqueous acetone, yielding diploschistesic acid as colourless leaflets (0·6 g.), m. p. 170° (decomp.) [Asahina and Yasue reported the m. p. as 174° (decomp.)] (Found: C, 57·4; H, 4·3. Calc. for $C_{16}H_{14}O_8$: C, 57·5; H, 4·2%). It gave a blue-violet colour with alcoholic ferric chloride.

The tetra-acetate, prepared by the method of Asahina and Yasue, crystallised from benzene as prisms, m. p. 164—165° (Found: C, 57·5; H, 4·1. Calc. for $C_{24}H_{22}O_{12}$: C, 57·4; H, 4·4%). Asahina and Yasue reported the same m. p.

Delhi University, India. [*Received, December 29th*, 1958.]

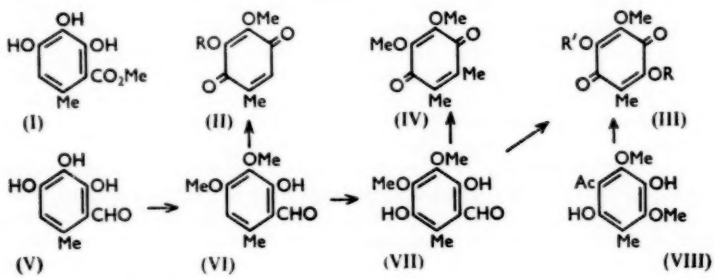
329. *New Synthesis of Fumigatin, Spinulosin Monomethyl Ethers, and Aurantiogliocladin.*

By T. R. Seshadri and G. B. Venkatasubramanian.

Fumigatin, spinulosin 3-methyl ether, and aurantiogliocladin have been prepared by using 3-hydroxyorcylaldehyde as the common C_8 intermediate. The hitherto unknown 6-monomethyl ether of spinulosin has also been made by the Dakin oxidation of 2 : 5-dihydroxy-4 : 6-dimethoxy-3-methylacetophenone.

Aghoramurthy and Seshadri [1] outlined a theory of biosynthesis of mould products involving C_8 units. As a typical example of toluquinones, fumigatin methyl ether (II; R = Me) was synthesised [2] starting from methyl 3-hydroxyorsellinate (I). We have now prepared fumigatin [3] (II; R = H), spinulosin 3-methyl ether [4] (III; R = H, R′ = Me) and aurantiogliocladin [5] (IV), employing 3-hydroxyorcylaldehyde (V) as common C_8 intermediate and simple reactions. These syntheses emphasise, not only the close relation among these compounds, but also their common origin; the methods involved are quite convenient.

Atranol is best prepared from lecanoric acid by a Gattermann reaction and decarboxylation.[6] By Dakin oxidation to 5-methylpyrogallol [7] and then a Gattermann reaction [8] this



gives the aldehyde (V). Partial methylation of (V) gives 2-hydroxy-3 : 4-dimethoxy-6-methylbenzaldehyde (VI), which is obtained in a better yield from the trimethyl ether of (V) by partial demethylation with anhydrous aluminium chloride in ether. The dimethyl ether (VI) was converted by successive Dakin oxidation and oxidation with ferric chloride into fumigatin (II; R = H). Alkaline persulphate oxidation of the dimethyl ether gave the quinol aldehyde (VII) which by Dakin oxidation yielded spinulosin 3-methyl ether (III; R = H, R′ = OMe). Clemmensen reduction of the quinol aldehyde (VII) yielded the quinol of aurantiogliocladin which was oxidised to aurantiogliocladin (IV) by ferric chloride as described by Vischer.[9]

In the above reactions Dakin oxidation of the quinol aldehyde (VII) gives the quinone (III; R = H, R′ = Me) directly. Examples of this type have been recorded previously.[10] By using this general reaction the hitherto unknown spinulosin 6-methyl ether (III; R′ = H, R = Me) has now been prepared from 2 : 5-dihydroxy-4 : 6-dimethoxy-3-methylacetophenone [11] (VIII) which however does not fall into the C_8 scheme.

[1] Aghoramurthy and Seshadri, *J. Sci. Ind. Res., India*, 1954, **13**, *A*, 114.
[2] *Idem, Chem. and Ind.*, 1954, 1327.
[3] Baker and Raistrick, *J.*, 1941, 670.
[4] Anslow and Raistrick, *J.*, 1939, 1446.
[5] Baker, *J.*, 1953, 824.
[6] Seshadri and Venkatasubramanian, preceding paper.
[7] Pfau, *Helv. Chim. Acta*, 1926, **9**, 650.
[8] Asahina and Yasue, *Ber.*, 1936, **69**, 2327.
[9] Vischer, *J.*, 1953, 815.
[10] Hassel and Todd, *J.*, 1947, 611; Jain and Seshadri, *Proc. Indian Acad. Sci.*, 1952, **35**, *A*, 233.

Experimental

2-Hydroxy-3 : 4-dimethoxy-6-methylbenzaldehyde (VI).—Atranol, obtained from lecanoric acid,[6] was converted by Dakin reaction into 5-methylpyrogallol[7] which by Gattermann synthesis yielded 2 : 3 : 4-trihydroxy-6-methylbenzaldehyde.[8] This with an excess of dimethyl sulphate and potassium carbonate in acetone gave the trimethyl ether (negative ferric reaction) as an oil which was partially demethylated as follows. A solution of it (1·5 g.) in ether (500 c.c.) was treated at 0° with a solution of anhydrous aluminium chloride (3 g.) in ether (20 c.c.). After 48 hr. at room temperature, the complex was decomposed with ice and dilute hydrochloric acid, warmed at 100° for ½ hr., and shaken with ether. The ether layer was extracted with 1% aqueous sodium hydroxide. Acidification of the alkaline extract gave a precipitate of the *dimethoxy-aldehyde* which crystallised from light petroleum (b. p. 60—80°) as needles (yield quantitative), m. p. 110° (Found: C, 61·1; H, 6·7. $C_{10}H_{12}O_4$ requires C, 61·2; H, 6·1%). It gave a violet-brown colour with alcoholic ferric chloride and a yellow solution in alkali.

The dimethoxy-aldehyde was obtained in poorer yield by partial methylation of the trihydroxy-aldehyde by 2 mols. of dimethyl sulphate and potassium carbonate (boiling for 3 hr.).

3 : 4-Dimethoxy-6-methylpyrocatechol.—A solution of the above dimethoxy-aldehyde (0·8 g.) in 4% aqueous sodium hydroxide (4 c.c.) was treated at 10° with a 6% solution (2 c.c.) of hydrogen peroxide and after 1 hr. acidification and extraction with ether gave the catechol (0·5 g.) which crystallised from light petroleum (b. p. 60—80°) as colourless aggregates of prisms, m. p. 101°. A mixed m. p. with a sample prepared according to the method of Baker and Raistrick[3] showed no depression.

Fumigatin (II; R = H).—The preceding ether was converted as described by Baker and Raistrick[3] into fumigatin, which crystallised from light petroleum as maroon-coloured needles, m. p. 112°. It exhibited all the colour reactions reported.

2 : 5-Dihydroxy-3 : 4-dimethoxy-6-methylbenzaldehyde (VII).—A solution of the above-mentioned dimethoxy-aldehyde (2·8 g.) in 10% aqueous sodium hydroxide (28 c.c.) was treated during 2 hr. at 10° with a saturated aqueous solution of potassium persulphate (4·4 g.). After 24 hr. at room temperature, the mixture was acidified to Congo Red with concentrated hydrochloric acid and extracted with ether to remove the unchanged aldehyde. The aqueous layer was treated with more concentrated hydrochloric acid (20 c.c.) and heated at 80° for ½ hr. The solution was then cooled, saturated with salt, and extracted with ether. The ether extract was dried and the solvent removed. The residual *quinol-aldehyde* crystallised from benzene–light petroleum (b. p. 60—80°) as pale yellow clusters of long, thin plates (1·3 g.), m. p. 130° (Found: C, 56·5; H, 5·9. $C_{10}H_{12}O_5$ requires C, 56·6; H, 5·7%). It gave a transient green colour with alcoholic ferric chloride.

Spinulosin 3-Methyl Ether (*6-Hydroxy-3 : 4-dimethoxytoluquinone*) (III; R = H, R′ = Me).—A solution of the quinol-aldehyde (VII) (0·4 g.) in 4% aqueous sodium hydroxide (3 c.c.) was treated with 6% hydrogen peroxide (2 c.c.) and left at 10° for ½ hr. The solution gradually became deep purple. It was acidified, filtered (deep red), saturated with sodium chloride, and continuously extracted with light petroleum (b. p. 60—80°). The extract was dried (Na_2SO_4) and the solvent removed. The residue crystallised from light petroleum as orange-red needles (0·2 g.), m. p. 108° (Found: C, 54·5; H, 5·4. Calc. for $C_9H_{10}O_5$: C, 54·5; H, 5·1%). Anslow and Raistrick[4] reported m. p. 105°.

On methylation with methyl sulphate–acetone–potassium carbonate, spinulosin dimethyl ether was obtained (m. p. 80°) agreeing in m. p. and colour reactions with the sample described by the above authors.

2 : 3-Dimethoxy-5 : 6-dimethylquinol.—A solution of 2 : 5-dihydroxy-3 : 4-dimethoxy-6-methylbenzaldehyde (0·4 g.) in alcohol (5 c.c.), concentrated hydrochloric acid (2 c.c.), and water (5 c.c.) was added to zinc amalgam (2 g.), and the mixture kept at 80° for ½ hr. The solution, initially yellow, slowly became colourless. The zinc was separated and the solution saturated with sodium chloride and repeatedly extracted with ether. The combined ether extracts were dried (Na_2SO_4) and the solvent was removed. The colourless oily residue was taken up in hot light petroleum (b. p. 60—80°) from which it crystallised as prisms (0·25 g.), m. p. 84° (Found: C, 60·8; H, 7·6. Calc. for $C_{10}H_{14}O_4$: C, 60·6; H, 7·1%). Brian *et al.*[12] who obtained it from aurantioglioclad in reported the same m. p.

[11] Murti, Seshadri, Sundaresan, and Venkataramani, *Proc. Indian Acad. Sci.*, 1957, **46**, *A*, 265.
[12] Brian, Curtis, Howland, Jefferys, and Raudnitz, *Experientia*, 1951, **7**, 266.

XUM

Aurantiogliocladin (IV).—Oxidation of the above quinol under the conditions described by Vischer [9] gave aurantiogliocladin, m. p. 63° (Found: C, 61·8; H, 5·8. Calc. for $C_{10}H_{12}O_4$: C, 61·2; H, 6·2%).

Spinulosin 6-Methyl Ether (*3-Hydroxy-4 : 6-dimethoxytoluquinone*) (III; R = Me, R′ = H).—Dakin oxidation of 2 : 5-dihydroxy-4 : 6-dimethoxy-3-methylacetophenone [11] (1 g.) under the conditions described earlier gave the *quinone methyl ether* which crystallised from light petroleum as broad, maroon-coloured, rectangular plates (0·5 g.), m. p. 75° (Found: C, 54·9; H, 5·0. $C_9H_{10}O_5$ requires C, 54·5; H, 5·1%). It gave a deep blue solution with concentrated sulphuric acid, a permanent pink colour with a trace of alkali, and a bluish-black colour with alcoholic ferric chloride. The identity was further confirmed by methylation to spinulosin dimethyl ether, m. p. and mixed m. p. 80°.

DELHI UNIVERSITY, INDIA. [*Received, December 29th*, 1958.]

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330. *The Structure of Palitantin.*

By K. BOWDEN, B. LYTHGOE, and D. J. S. MARSDEN.

Palitantin is shown to have the structure (XV) and the probable configuration expressed in formula (XXVIII). An explanation is provided of the unusual substitution reaction between iodine and palitantin.

THE neutral optically active metabolite palitantin, $C_{14}H_{22}O_4$, was isolated by Birkinshaw and Raistrick [1] from culture filtrates of *Penicillium palitans* Westling; it is also produced by strains of *P. frequentans* [2] and *P. cyclopium*.[3] Careful experimental work by the discoverers,[1] later extended by Birkinshaw,[4] revealed its principal reactions and established some of its major structural features. Because some of its reactions had a possible bearing on our other work we became interested in palitantin, and Professors Birkinshaw and Raistrick most generously encouraged us to continue their studies. We now describe additional experiments which serve to define its structure.

The earlier [1] work showed that palitantin contains a reactive carbonyl group, regarded as aldehydic because oxidation with Doeuvre's reagent [5] (alkaline potassium mercuri-iodide) gave palitantic acid, $C_{14}H_{22}O_5$. Palitantin formed a di-*p*-bromobenzoate, showing the presence of two hydroxyl groups; the fourth oxygen atom was not definitely characterised, but there was some evidence that it, too, was hydroxylic. This is now confirmed by the well-defined band $\nu_{max.}$ 3500 cm.$^{-1}$ shown by the di-*p*-bromobenzoate. Catalytic reduction of palitantin gave tetrahydropalitantin, which retains the original carbonyl function and was oxidised to tetrahydropalitantic acid; palitantin therefore contains two ethylenic links and one carbocyclic ring. One of the ethylenic links is present in the group $Pr^n{\cdot}CH{:}C<$, since ozonolysis [4] of palitantic acid gave butyraldehyde.

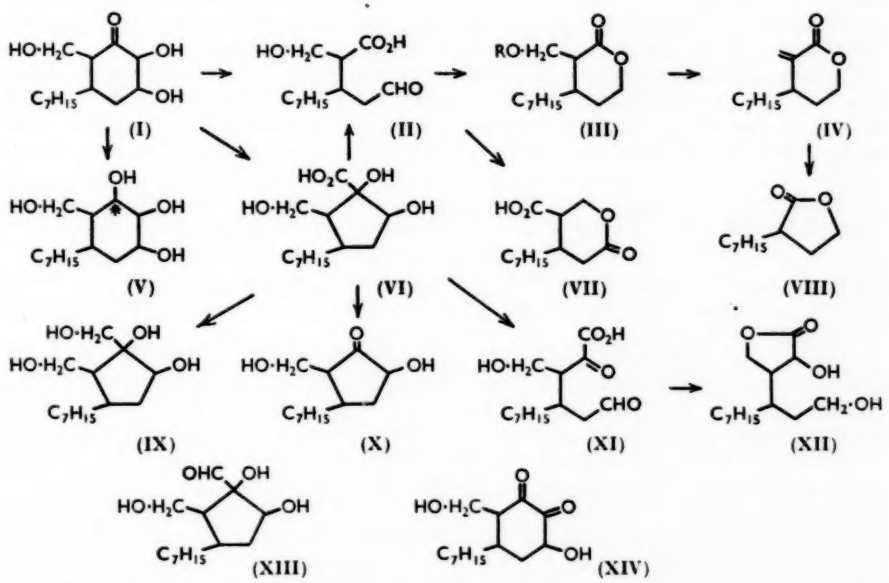
Birkinshaw [4] studied the behaviour of tetrahydropalitantin and tetrahydropalitantic acid towards periodate; the acid reduced only 1 mol. of oxidant, forming two new carbonyl groups. One of these was recognised as part of an α-keto-acid structure, so accounting for its resistance to further oxidation. By contrast, tetrahydropalitantin reduced 2 mols. of oxidant, giving formic acid and a syrupy aldehydo-acid. This was oxidised to a syrupy lactonic acid by Doeuvre's reagent, and then characterised as the dihydrazide of the corresponding hydroxy-dibasic acid $C_{13}H_{24}O_5$. Oxidation of the lactonic acid with nitric acid gave (+)-heptylsuccinic acid; this was identified by comparison with the synthetic racemic acid without the assistance of infrared methods; our own experiments provide an indirect confirmation that this identification is correct. Birkinshaw [4] suggested that

[1] Birkinshaw and Raistrick, *Biochem. J.*, 1936, **30**, 801.
[2] Curtis, Hemming, and Smith, *Nature*, 1951, **167**, 557.
[3] Bracken, Pocker, and Raistrick, *Biochem. J.*, 1954, **57**, 587.
[4] Birkinshaw, *ibid.*, 1952, **51**, 271.
[5] Doeuvre, *Bull. Soc. chim. France*, 1927, **41**, 1145.

XUM

palitantin contains a *cyclo*hexane ring bearing heptyl and formyl substituents, and with hydroxyl groups situated α and β to the formyl group.

We commenced the present work by deducing the structure (II) for the aldehydo-acid, $C_{13}H_{24}O_4$, formed by periodate oxidation of tetrahydropalitantin. The aldehydo-acid showed no tendency to lactonise, whereas the dibasic acid obtained from it by oxidation is completely lactonic;[4] clearly the lactone ring involves the newly generated carboxyl group [structure (VII)]. Sodium borohydride reduced the aldehydo-acid to a crystalline δ-lactone (III; R = H), $\nu_{max.}$ 1718 cm.$^{-1}$; this lactonisation involved the newly generated hydroxyl function, not that which pre-existed in the aldehydo-acid. The presence of the latter hydroxyl group in the δ-lactone (III; R = H) was shown by the formation of a crystalline toluene-*p*-sulphonate. When warmed with pyridine this lost toluene-*p*-sulphonic acid, giving an αβ-unsaturated δ-lactone (IV), $\lambda_{max.}$ 212 mμ, $\nu_{max.}$ 1733 (conjugated lactonic C:O), 1631 cm.$^{-1}$ (conjugated C:C). Ozonolysis gave formaldehyde, showing that the unsaturated lactone contains an α-methylene group; it is therefore of interest that the lactone showed no C–H deformation band near 900 cm.$^{-1}$, but instead showed bands at 943 and 803 cm.$^{-1}$; similar behaviour has been recorded for 2-methylenedodecanoic acid.[6] When in the above ozonolysis the ozonide was decomposed with hydrogen peroxide–acetic acid, an optically active γ-lactone (VIII), $\nu_{max.}$ 1780 cm.$^{-1}$, was formed; after purification through the crystalline hydrazide it showed infrared absorption identical with that of synthetic (±)-α-heptyl-γ-butyrolactone.[7] The active lactone was racemised with hot ethanolic sodium ethoxide and converted into the corresponding hydrazide, which was identical with that prepared from the (±)-lactone. These reactions establish that the aldehydo-acid has the structure (II).



Only two structures for tetrahydropalitantin, (I) and (XIII), are compatible with the formation of the aldehydo-acid (II); of these, structure (XIII) represents the aldehyde corresponding to the acid (VI). There is no doubt that structure (VI) correctly represents tetrahydropalitantic acid. A Curtius degradation of this acid gave the five-membered

[6] Freeman, *J. Amer. Chem. Soc.*, 1953, **75**, 1861.
[7] Rothstein, *Bull. Soc. chim. France*, 1935, **2**, 80.

cyclic ketone (X), $\nu_{max.}$ 1742 cm.$^{-1}$. Moreover, the α-keto-acid (XI), which Birkinshaw [4] obtained by periodate oxidation of tetrahydropalitantic acid, was reduced by sodium borohydride to a γ-lactone (XII), $\nu_{max.}$ 1780 cm.$^{-1}$. Tetrahydropalitantic acid reduced 2 mols. of lead tetra-acetate, giving the aldehydo-acid (II), identified by conversion into the crystalline toluene-*p*-sulphonate (III; R = *p*-$C_6H_4Me{\cdot}SO_2$). Finally, lithium aluminium hydride reduced methyl tetrahydropalitantate to the tetraol (IX), which consumed 2 mols. of periodate, giving 1 mol. of formaldehyde together with the aldehydo-acid (II).

Since tetrahydropalitantic acid has the structure (VI) it would be natural to conclude that tetrahydropalitantin has the structure (XIII); however, this is untenable for the following reasons. Birkinshaw and Raistrick [1] showed, and we have confirmed, that reduction of the carbonyl function of tetrahydropalitantin with sodium amalgam gives *two* tetraols $C_{14}H_{28}O_4$, here referred to as α- and β-tetrahydropalitantol. The β-isomer, more readily obtained by reduction with sodium borohydride, has been characterised as the tetra-*p*-bromobenzoate. Neither isomer is identical with the tetraol (IX) obtained from tetrahydropalitantic acid. This acid thus has a different carbon skeleton from tetrahydropalitantin, which must be the ketone (I); the tetrahydropalitantols are clearly the diastereoisomers (V). In agreement with this, the β-isomer reduced 2 mols. of periodate, giving formic acid, but no formaldehyde.

The ketonic structure (I) agrees well with the infrared absorption of tetrahydropalitantin, which shows $\nu_{max.}$ 1706 cm.$^{-1}$ but no aldehydic band near 2800 cm.$^{-1}$. A molecular rearrangement analogous to the benzilic acid change must occur in the formation of tetrahydropalitantic acid. It is possible that the α-diketone (XIV) may be an intermediate, although under similar conditions Doeuvre's reagent converted adipoin only into *cyclo*hexane-1 : 2-dione, which requires more vigorous alkaline treatment for rearrangement [8] to 1-hydroxy*cyclo*pentanecarboxylic acid. The palitantic acid rearrangement is stereospecific, only one of the two possible diastereoisomers being isolated.

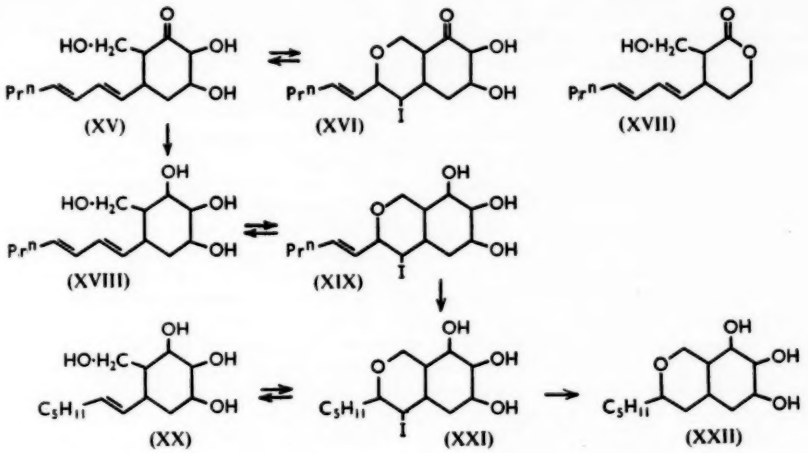
Turning now from the saturated to unsaturated compounds, we note that palitantin has $\lambda_{max.}$ 232 mμ (ε 34,000). Palitantol, the tetraol obtained from it by reduction with sodium amalgam [9] or, better, with sodium borohydride, shows similar absorption, which is thus dienoid. In view of the earlier isolation [4] of butyraldehyde on ozonolysis of palitantic acid, palitantin therefore contains the system $Pr^n{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}$ and has the structure (XV). Palitantin and its dienoid relatives show $\nu_{max.}$ 990 (conjugated *trans*-CH:CH) and 942 cm.$^{-1}$; a band of the latter frequency is present [10] in the spectra of dienes with one *cis*- and one *trans*-double bond, but the corresponding saturated compounds of the palitantin series also showed a similar band, so this type of diene system is not necessarily present in palitantin; indeed we regard it as improbable in view of the high intensity of the 232 mμ absorption.

Birkinshaw [4] showed that palitantin and palitantic acid are substituted by iodine, giving monoiodo-compounds. We have studied this unusual reaction, which we found to take place also with palitantol (XVIII) and with the diunsaturated δ-lactone (XVII) obtained from palitantin by periodate oxidation followed by reduction with sodium borohydride. During the reaction the dienoid light absorption was lost and a hydroxyl group was masked; for example, the product from the δ-lactone (XVII) contained no free hydroxyl group. The reaction is therefore a cyclisation between one of the double bonds and the hydroxymethyl group, and iodopalitantin has the cyclic iodo-ether structure (XVI). In agreement with this, it was reconverted into palitantin by zinc and acetic acid. Addition of the elements of an alkyl hypoiodite to a double bond is not normally possible, and the present example illustrates the favourable effect on reaction velocity often observed when two reacting groups occupy sterically suitable positions within the same molecule.

In further confirmation of the proposed structures iodopalitantol (XIX) absorbed 1 mol.

[8] Wallach, *Annalen*, 1924, **437**, 148.
[9] Curtis and Duncanson, *Biochem. J.*, 1952, **51**, 276.
[10] Cf. Crombie, *J.*, 1955, 1007.

of hydrogen (palladium), giving the saturated iodo-ether (XXI); further hydrogenation in the presence of aqueous alkali gave the iodine-free cyclic ether (XXII); iodopalitantin



underwent similar reactions. Zinc and acetic acid converted the iodo-ether (XXI) into the monounsaturated compound (XX), which on treatment with iodine gave back the iodo-ether (XXI); the cyclisation does not require a diene system for its success. The structure of the product (XX) was shown by ozonolysis, which gave hexanal. These reactions provided means of studying the component double bonds of the diene system of palitantin in isolation from each other. The compounds (XVI) and (XIX) showed very strong bands near 960 cm.$^{-1}$, which disappeared on hydrogenation, so that the double bond remote from the ring in palitantin undoubtedly has the *trans*-configuration. The monounsaturated tetraol (XX) gave a somewhat less clear picture; it showed a band of moderate intensity at 959 cm.$^{-1}$; we conclude that the double bond proximate to the ring in palitantin is probably of the *trans*-type.

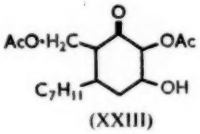
It was of interest to prepare partially protected derivatives of palitantin; acetylation readily gave a diacetate, but no well-defined triacetate. The diacetate probably has the structure (XXIII), since it failed to undergo the cyclic iodo-ether reaction, and was recovered after treatment with periodate. The resistance of the third hydroxyl group to acylation is connected with the presence of the keto-group in palitantin and tetrahydropalitantin; in tetrahydropalitantol all four hydroxyl groups are reactive. Palitantin, tetrahydropalitantin, iodopalitantin, and iodopalitantic acid (XXIV) readily formed crystalline *iso*propylidene derivatives; it may be inferred that the reaction giving *iso*propylidenepalitantin (XXV) does not involve the primary hydroxyl group.

Although we have not attempted a detailed study of the stereochemistry of palitantin, some of our observations are relevant to it, and we point out the conclusions which may, with due reserve, be drawn from them. It is probable that (+)-heptylsuccinic acid belongs to the same configurational series as *D*(+)-methylsuccinic acid (XXVI) and *D*(+)-*iso*propylsuccinic acid;[11] this defines the absolute configuration at the carbon atom bearing the heptadienyl group. Iodopalitantin semicarbazone gave back iodopalitantin on treatment with pyruvic acid, so that the two six-membered rings in the iodo-compound probably have the stable *trans*-fusion; *i.e.*, the hydroxymethyl and the heptadienyl group of palitantin are *trans*-related. The non-primary hydroxyl groups of

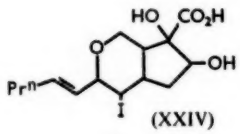
[11] Fredga, *Arkiv Kemi Min. Geol.*, 1942, **15**, *B*, No. 23.

palitantin and palitantic acid, which react with acetone, are almost certainly *cis*-related. Since palitantic acid shows no tendency to lactone formation its carboxyl and hydroxymethyl groups are probably *trans*-related. These considerations lead to the complete stereostructures (XXVII) and (XXVIII) for palitantic acid and palitantin respectively.

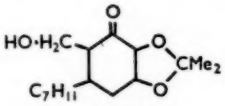
It may be noted that the structure (XV) for palitantin could readily be derived biogenetically from acetate residues, as are many other mould metabolites.[12]



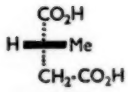
(XXIII)



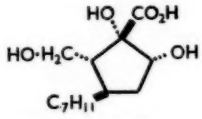
(XXIV)



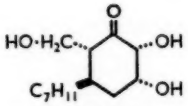
(XXV)



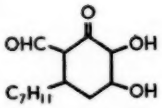
(XXVI)



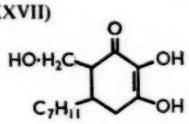
(XXVII)



(XXVIII)



(XXIX)



(XXX)

Finally, mention must be made of the acidic (enolic) compound frequentin, $C_{14}H_{20}O_4$, first isolated from *P. palitans* [1] and later from *P. frequentans*.[2] Curtis and Duncanson [9] showed that frequentin, $\nu_{max.}$ 1732, shoulder at 1720 cm.$^{-1}$, is reduced by sodium amalgam to "dihydropalitantin," *i.e.*, palitantol. Frequentin is clearly an enolised α- or β-dicarbonyl compound, and in the light of the present work two structures (XXIX) and (XXX) are possible; of these we prefer the latter.

Experimental

Ultraviolet spectra were taken in ethanol.

Palitantin.—Culture filtrates from a strain of *P. cyclopium* (freshly isolated from soil), grown [3] at 24° for 14 days on Czapek–Dox medium, were extracted with chloroform, the chloroform evaporated, and the residue crystallised first from benzene and then from water, giving palitantin (250 mg./l. of medium), m. p. 164—165° (lit.,[1] 165°) (Found: C, 66·0; H, 8·6. Calc. for $C_{14}H_{22}O_4$: C, 66·1; H, 8·7%), $\lambda_{max.}$ 232 mμ (ε 34,000), $\nu_{max.}$ (in KCl) 3333, 1715, 984, 956 cm.$^{-1}$.

Its identity was confirmed by conversion [1] into tetrahydropalitantin, m. p. 116° (lit.,[1] 116°) and palitantic acid, m. p. 146° (lit.,[1] 146—148°), $\lambda_{max.}$ 232 mμ (ε 29,000).

Degradation of Tetrahydropalitantin to the δ-Lactone (III; R = H).—Tetrahydropalitantin (1 g.) in ethanol (50 c.c.) was kept for 18 hr. with aqueous 0·1M-sodium metaperiodate (120 c.c.). Extraction with ether gave the crude syrupy aldehydo-acid, which required for neutralisation at 18° 0·94 equiv. of 0·02N-sodium hydroxide. The aldehydo-acid was reduced at 20° with sodium borohydride (1 g.) in methanol (20 c.c.). The solution was diluted with water and extracted with ether, and the aqueous phase acidified and extracted with chloroform. Evaporation of the chloroform and crystallisation from light petroleum (b. p. 60—80°) gave the *δ-lactone* as plates (500 mg.), m. p. 46°, $[\alpha]_D^{18}$ −19° (in alcohol), $\nu_{max.}$ (in Nujol) 3460, 1723 cm.$^{-1}$ (Found: C, 68·1; H, 10·4. $C_{13}H_{24}O_3$ requires C, 68·4; H, 10·6%). At 18° the lactone did not react in aqueous alcohol with 0·02N-sodium hydroxide; titration at 80° gave neutralisation equivalent 231 ($C_{13}H_{24}O_3$ requires 228).

[12] Birch and Donovan, *Austral. J. Chem.*, 1953, **6**, 360; and later papers by Birch and his co-workers.

Degradation of the δ-Lactone to (−)-α-Heptylbutyrolactone.—The δ-lactone (150 mg.), toluene-*p*-sulphonyl chloride (250 mg.), pyridine (0·2 c.c.), and chloroform (5 c.c.) were kept together at 18° for 18 hr. and the mixture worked up in the usual manner, giving the *toluene*-p-*sulphonate* (170 mg.) as plates [from ethyl acetate–light petroleum (b. p. 60—80°)], m. p. 76° (Found: C, 62·7; H, 7·8. $C_{20}H_{30}O_5S$ requires C, 62·8; H, 7·9%). A portion (120 mg.) was kept at 80° in pyridine (5 c.c.) for 2 hr., and the cooled solution diluted with ether and washed with dilute hydrochloric acid and with water. Evaporation gave the crude α-methylene-δ-lactone as an oil (61 mg.), $\lambda_{max.}$ 212 mμ (ε 6000), which absorbed 0·85 mol. of hydrogen (palladised charcoal). Ozonolysis at 0° of this oil (230 mg.) in glacial acetic acid (6 c.c.) and ethyl acetate (4 c.c.), followed by steam-distillation and treatment of the distillate with dimedone gave formaldehyde dimethone (125 mg.), m. p. and mixed m. p. 189°.

The α-methylene-δ-lactone (200 mg.) was similarly ozonised at −25°, and the solution then heated under reflux for 2 hr. with water (2 c.c.) and 30% hydrogen peroxide (1 c.c.). The cooled solution was diluted with water and extracted with chloroform, and the extract washed with aqueous sodium thiosulphate, aqueous sodium carbonate, and water, then dried and evaporated. The neutral oil (140 mg.) and ethanolic hydrazine hydrate gave the *hydrazide* of (−)-α-heptyl-γ-hydroxybutyric acid (140 mg.) as needles (from dilute alcohol), m. p. 138°, $[\alpha]_D^{18}$ −21° (in pyridine) (Found: C, 61·0; H, 11·0; N, 13·4. $C_{11}H_{24}O_2N_2$ requires C, 61·1; H, 11·2; N, 12·95%). The hydrazide was kept at 100° for 30 min. with 8N-sulphuric acid; extraction with chloroform gave (−)-α-heptylbutyrolactone as an oil, $[\alpha]_D^{18}$ −12° (in chloroform); its infrared spectrum was identical with that of synthetic (±)-α-heptylbutyrolactone.[7]

The (−)-lactone (120 mg.) and N-ethanolic sodium ethoxide (2·5 c.c.) were heated under reflux for 2 hr.; acidification and extraction with ether gave the racemic lactone, $[\alpha]_D^{18}$ 0° ± 0·2° (in chloroform). It was converted into the (±)-*hydrazide* which separated from aqueous alcohol as needles, m. p. 127—127·5° (Found: C, 60·7; H, 10·95; N, 13·15%), undepressed on admixture with material of m. p. 127—127·5° prepared from the synthetic (±)-lactone.

Curtius Degradation of Tetrahydropalitantic Acid.—Tetrahydropalitantic acid [1] (250 mg.) was suspended in 0·01N-ethereal diazomethane (100 c.c.); after 5 min. the solvent was removed and the residue crystallised from benzene–light petroleum (b. p. 60—80°), giving the *methyl ester monohydrate* (220 mg.), m. p. 80—81° (Found: C, 58·5; H, 9·7. $C_{15}H_{28}O_5,H_2O$ requires C, 58·8; H, 9·9%). Sublimation at 75°/10^{-4} mm. gave anhydrous material, m. p. 83—84° (Found: C, 62·9; H, 9·7. $C_{15}H_{28}O_5$ requires C, 62·5; H, 9·8%). The *hydrazide*, obtained from the methyl ester in the usual way, separated from methanol as needles, m. p. 207—208° (Found: C, 58·8; H, 9·7; N, 9·4. $C_{14}H_{28}O_4N_2$ requires C, 58·3; H, 9·8; N, 9·7%). A portion (170 mg.) in N-hydrochloric acid was shaken with ether (10 c.c.) and aqueous sodium nitrite (700 mg. in 4 c.c.) at 0°. The ethereal layer was separated, the aqueous layer was re-extracted with ether, and the united ethereal layers were washed with aqueous sodium hydrogen carbonate and water, and dried. Alcohol (20 c.c.) was added, the ether was evaporated, and the solution heated under reflux for 2 hr. Evaporation and crystallisation from benzene gave a *substance* (36 mg.), m. p. 172° (Found: C, 61·8; H, 9·7; N, 5·0. $C_{14}H_{25}O_4N$ requires C, 62·0; H, 9·3; N, 5·2%). The mother-liquors were diluted with light petroleum (b. p. 60—80°), and the product recrystallised from that solvent, giving the *ketone* (X) as plates (44 mg.), m. p. 69° (Found: C, 68·1; H, 10·4. $C_{13}H_{24}O_3$ requires C, 68·4; H, 10·6%).

Oxidative Degradation of Tetrahydropalitantic Acid.—(*a*) The acid (274 mg.) and 0·05M-chloroformic lead tetra-acetate (50 c.c.) were kept for 24 hr. (uptake 1·9 mol.), and the solution was washed with water and freed from precipitated lead dioxide. It was extracted with aqueous sodium hydrogen carbonate, which was then acidified, and the product extracted with chloroform and reduced in methanol (15 c.c.) with sodium borohydride (0·4 g.). The diluted solution was extracted with ether, then acidified and extracted with chloroform. Evaporation of the chloroform and crystallisation from light petroleum (b. p. 60—80°) gave the δ-lactone (III; R = H) (70 mg.), m. p. 43°, $[\alpha]_D^{18}$ −19° (in alcohol). It was further identified by conversion into the toluene-*p*-sulphonate, m. p. and mixed m. p. 76°.

(*b*) The acid (1 g.) was oxidised [4] with sodium metaperiodate (uptake 1 mol.), the product isolated with ether, and a portion (240 mg.) reduced in methanol (20 c.c.) with sodium borohydride (500 mg.). Isolation in the usual manner gave a neutral oily lactone (200 mg.), $\nu_{max.}$ 1783 $cm.^{-1}$.

The Tetraol (IX).—Methyl tetrahydropalitantate (500 mg.) in ether (50 c.c.) was added

slowly with stirring to lithium aluminium hydride (1·5 g.) in ether (100 c.c.). The stirred mixture was heated under reflux for 3 hr., then cooled, and the excess of hydride was destroyed cautiously with ethyl acetate (10 c.c.) followed by saturated aqueous ammonium chloride (12 c.c.). The mixture was filtered and the filtrate evaporated; it left no residue. The precipitate was dissolved in dilute hydrochloric acid and the product isolated with chloroform. Crystallisation from benzene–*cyclo*hexane gave the *tetraol* (180 mg.) as needles, m. p. 46°, $[\alpha]_D^{18}$ −78° (in alcohol) (Found: C, 64·6; H, 10·5. $C_{14}H_{28}O_4$ requires C, 64·6; H, 10·8%).

The tetraol (160 mg.) was kept for 4 hr. with 0·1M-sodium metaperiodate (25 c.c.) (uptake, 2·0 mol.), and an aliquot part (10 c.c.) treated with sodium acetate and dimedone, giving formaldehyde dimethone (0·9 mol.), m. p. and mixed m. p. 189—190°. The remainder of the solution was extracted with ether, giving an oil (120 mg.) which was reduced in methanol (5 c.c.) with sodium borohydride (200 mg.). Isolation in the usual manner gave the δ-lactone (III; R = H) (80 mg.), m. p. and mixed m. p. 45°, $[\alpha]_D^{20}$ −19° (in chloroform).

β-*Tetrahydropalitantol*.—To tetrahydropalitantin (500 mg.) in methanol (15 c.c.) sodium borohydride (200 mg.) was added during ½ hr. The product, isolated in the usual way, separated from ether as plates (400 mg.), m. p. 96° (lit.,[1] 98—99°) (Found: C, 64·4; H, 10·6. Calc. for $C_{14}H_{28}O_4$: C, 64·6; H, 10·8%). The *tetra*-p-*bromobenzoate* separated from dilute alcohol as needles, m. p. 151—152° (Found: C, 50·9; H, 4·0; Br, 32·3. $C_{42}H_{40}O_8Br_4$ requires C, 50·8; H, 4·0; Br, 32·2%).

β-Tetrahydropalitantol reduced 1·9 mols. of sodium metaperiodate in 48 hr., giving a neutral oil and 0·5 equiv. of formic acid. When lead tetra-acetate was the oxidant 2·0 mols. were reduced rapidly, giving as the product a neutral oil.

Palitantol.—Reduction with sodium borohydride in methanol in the usual way converted palitantin (500 mg.) into palitantol (400 mg.) which separated from water as plates, m. p. 171—172° (lit.,[9] 170—171°), $[\alpha]_D^{18}$ −53° (in alcohol) (Found: C, 65·6; H, 9·3. Calc. for $C_{14}H_{24}O_4$: C, 65·6; H, 9·4%), $\lambda_{max.}$ 231 mμ (ε 32,000), $\nu_{max.}$ (in KCl), 3280, 992, 960 cm.$^{-1}$. Hydrogenation (uptake 2·0 mols.) in alcohol (palladised charcoal) gave β-tetrahydropalitantol, m. p. and mixed m. p. 96°.

Reactions of Iodopalitantin.—Prepared by Birkinshaw's [4] method, iodopalitantin had m. p. 136° (decomp.), $[\alpha]_D^{18}$ −28° (in chloroform) (Found: C, 44·1; H, 5·5. Calc. for $C_{14}H_{21}O_4I$: C, 44·2; H, 5·6%), $\lambda_{max.}$ 262 mμ (ε 900), $\nu_{max.}$ (in Nujol) 3413, 1724, 959 cm.$^{-1}$.

Iodopalitantin (100 mg.), zinc dust (1 g.), acetic acid (1 c.c.), and alcohol (5 c.c.) were kept under reflux for 1 hr. and filtered. The filtrate was diluted with chloroform, washed with aqueous sodium carbonate, dried, and evaporated. Crystallisation from water gave palitantin (55 mg.), m. p. and mixed m. p. 163°.

Iodopalitantin semicarbazone (41 mg.), m. p. 228° (decomp.) (Found: C, 41·3; H, 5·4; N, 9·5. $C_{15}H_{24}O_4N_3I$ requires C, 41·2; H, 5·4; N, 9·6%), and pyruvic acid (300 mg.) in glacial acetic acid (5 c.c.) and water (0·5 c.c.) were kept at 80° for 45 min., the cooled mixture extracted with chloroform, and the extract washed with aqueous sodium hydrogen carbonate and water, and evaporated. Crystallisation from water gave iodopalitantin, m. p. 136° (decomp.), $[\alpha]_D^{18}$ −29° (in chloroform). In one experiment a second crystalline form, m. p. 151° (decomp.), was obtained; it had the same optical rotation and furnished on hydrogenation the dihydro-compound, m. p. 147—148° (see below).

Hydrogenation (uptake 1·0 mol.) of iodopalitantin in ethyl acetate (5% palladised charcoal) gave quantitatively the *dihydro-compound*. It separated from dilute alcohol as plates, m. p. 147—148°, $[\alpha]_D^{20}$ −23° (in alcohol) (Found: C, 44·2; H, 6·0. $C_{14}H_{23}O_4I$ requires C, 44·0; H, 6·1%), $\lambda_{max.}$ 259 mμ (ε 900), no $\nu_{max.}$ near 950 cm.$^{-1}$. Hydrogenation (uptake 1·0 mol.) of a portion (35 mg.) in alcohol containing 1 equiv. of aqueous sodium hydroxide with the same catalyst gave the *deiodo-compound* (20 mg.) as needles (from dilute alcohol), m. p. 129° (Found: C, 65·6; H, 9·6. $C_{14}H_{24}O_4$ requires C, 65·6; H, 9·4%).

Iodopalitantol.—Prepared similarly to iodopalitantin, from palitantol (500 mg.), *iodopalitantol* (350 mg.) formed hydrated plates (from dilute alcohol), m. p. 145° (decomp.), $[\alpha]_D^{18}$ −101° (in chloroform) (Found: C, 42·1; H, 6·2. $C_{14}H_{23}O_4I,H_2O$ requires C, 42·0; H, 6·3%), $\lambda_{max.}$ 260 mμ (ε 800) $\nu_{max.}$ (in Nujol) 960 cm.$^{-1}$. The *dihydro-compound* formed hydrated needles (from dilute alcohol), m. p. 126° (Found: C, 41·4; H, 6·7. $C_{14}H_{25}O_4I,H_2O$ requires C, 41·8; H, 6·8%). Further hydrogenation in the presence of alkali gave the *deiodo-compound* which separated from benzene as hydrated needles, m. p. 112° (Found, in material dried at 80°/0·1 mm.: C, 65·3; H, 9·5. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·1%).

Treatment of iodopalitantol with zinc dust in ethanol–acetic acid, as described for iodopalitantin, gave palitantol, m. p. and mixed m. p. 171°, $\lambda_{max.}$ 231 mμ (ε 31,000). Similar treatment of the dihydro-compound (m. p. 126°) gave the *product* (XIX) as plates (from ethyl acetate), m. p. 154—156° (Found: C, 65·0; H, 10·0. $C_{14}H_{26}O_4$ requires C, 65·1; H, 10·1%), $\nu_{max.}$ (in $CHCl_3$) 959 cm.$^{-1}$. Ozonolysis of this product (80 mg.) gave hexanal, isolated as the 2 : 4-dinitrophenylhydrazone (30 mg.), m. p. and mixed m. p. 106° (Found: C, 51·5; H, 6·0. Calc. for $C_{12}H_{16}O_4N_4$: C, 51·4; H, 5·8%).

The Iodo-derivative of the δ-Lactone (XVII).—The *δ-lactone* (250 mg.), prepared from palitantin (500 mg.) as described for the saturated analogue, separated from ether–light petroleum (b. p. 60—80°) as needles, m. p. 78°, $[\alpha]_D^{18}$ −25° (in alcohol) (Found: C, 69·1; H, 8·8. $C_{13}H_{20}O_3$ requires C, 69·6; H, 9·0%), $\lambda_{max.}$ 231 mμ (ε 29,000), $\nu_{max.}$ (in Nujol) 3378, 1706, 983 cm.$^{-1}$. The *toluene*-p-*sulphonate*, plates [from ether–light petroleum (b. p. 40—60°)], had m. p. 94° (Found: C, 63·6; H, 6·8. $C_{20}H_{26}O_5S$ requires C, 63·5; H, 6·9%).

The δ-lactone (200 mg.) gave in the usual way an *iodo-derivative* (80 mg.) which separated from ether as plates, m. p. 78°, $[\alpha]_D^{18}$ −55° (in chloroform) (Found: C, 44·9; H, 5·5. $C_{13}H_{19}O_3I$ requires C, 44·6; H, 5·5%), $\lambda_{max.}$ 258 mμ (ε 840), no hydroxyl band near 3500 cm.$^{-1}$, $\nu_{max.}$ (in Nujol) 1733, 983 cm.$^{-1}$. The *dihydro-compound* separated from light petroleum (b. p. 40—60°) as needles, m. p. 53—54° (Found: C, 44·9; H, 6·0. $C_{13}H_{21}O_3I$ requires C, 44·3; H, 6·0%).

Palitantin Diacetate.—Palitantin (250 mg.), acetic anhydride (0·6 c.c.), pyridine (0·3 c.c.), and chloroform (5 c.c.) were kept together at room temperature for 18 hr. and the product was isolated in the usual way, giving the *diacetate* (200 mg.) as plates [from benzene–light petroleum (b. p. 40—60°)], m. p. 157—158° (Found: C, 64·0; H, 7·75. $C_{18}H_{26}O_6$ requires C, 63·9; H, 7·7%), $\lambda_{max.}$ 232 mμ (ε 34,000), $\nu_{max.}$ (in Nujol) 3546, 1733, 1718, 988 cm.$^{-1}$. Prepared similarly, *tetrahydropalitantin diacetate* had m. p. 120—121° (Found: C, 62·8; H, 8·2. $C_{18}H_{30}O_6$ requires C, 63·1; H, 8·8%).

iso*Propylidene Derivatives.*—(*a*) Tetrahydropalitantin (100 mg.) and freshly fused zinc chloride (400 mg.) were heated for 10 min. under reflux with dry acetone (50 c.c.) and enough glacial acetic acid to give homogeneity. The cooled mixture was diluted with water, extracted with chloroform, and the extract washed, dried, and evaporated. Crystallisation from ether–light petroleum (b. p. 40—60°) gave the *product* (90 mg.) as needles, m. p. 79° (Found: C, 68·5; H, 10·3. $C_{17}H_{30}O_4$ requires C, 68·4; H, 10·1%).

(*b*) Similarly prepared, OO-iso*propylidenepalitantin* formed needles, m. p. 108° (Found: C, 69·0; H, 8·9. $C_{17}H_{26}O_4$ requires C, 69·35; H, 8·9%), $\lambda_{max.}$ 228 mμ (ε 34,500), $\nu_{max.}$ (in Nujol) 3460, 1727, 980 cm.$^{-1}$.

(*c*) Iodopalitantin similarly gave an iso*propylidene derivative*, m. p. 117—118°, $[\alpha]_D^{20}$ −38° (in alcohol) (Found: C, 48·45; H, 6·15. $C_{17}H_{25}O_4I$ requires C, 48·6; H, 6·0%).

(*d*) The iso*propylidene derivative* of iodopalitantic acid formed cubes [from light petroleum (b. p. 40—60°)], m. p. 154—155° (Found: C, 46·8; H, 5·9. $C_{17}H_{25}O_5I$ requires C, 46·8; H, 5·8%).

We express our deep gratitude to Professor J. H. Birkinshaw and Professor H. Raistrick, F.R.S., for providing cultures of *P. palitans* and *P. cyclopium*, and to Mr. G. Smith for assistance in identifying cultures. One of us (D. J. S. M.) thanks the Department of Scientific and Industrial Research for a Research Studentship.

THE UNIVERSITY, LEEDS, 2. [*Received, December* 31*st*, 1958.]

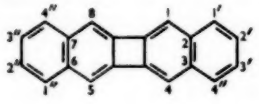
331. *The Synthesis of* 2 : 3-6 : 7-*Dibenzodiphenylene.*

By R. F. Curtis and G. Viswanath.

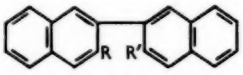
The synthesis of 2 : 3-6 : 7-dibenzodiphenylene (I) from 3-nitro-2-naphthylamine is described. Proof of structure follows from reduction to 2 : 2′-dinaphthyl. 3-Nitro-2-naphthylamine was prepared by dehydrogenation of 6-acetamido-1 : 2 : 3 : 4-tetrahydro-7-nitronaphthalene.

Attempts to prepare the corresponding 1′ : 2′ : 3′ : 4′ : 1″ : 2″ : 3″ : 4″-octahydro-2 : 3-6 : 7-dibenzodiphenylene were unsuccessful; dehydrogenation gave the same 2 : 3-6 : 7-dibenzodiphenylene (I). The preparation of 1′ : 2′ : 3′ : 4′ : 1″ : 2″ : 3″ : 4″-octahydro-2 : 3-6 : 7-dibenzocarbazole (V) and dinaphtho(2′ : 3′-2 : 3)(2″ : 3″-4 : 5)furan (VIII) is also recorded.

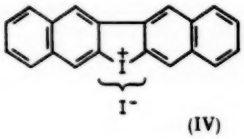
Diphenylene has been extensively investigated,[1] but attempts to synthesise the corresponding naphthalene derivatives, *e.g.*, 2 : 3-6 : 7-dibenzodiphenylene (I) (and three other possible isomers), have failed until recently. Rosenhauer and his co-workers [2] heated 1 : 4-naphthaquinone in anhydrous pyridine and obtained a quinonoid compound which on zinc dust distillation gave a hydrocarbon formulated as (I) but later shown [3] to be trinaphthylene.



(I)



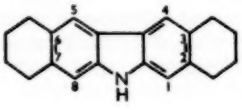
(II); R = R′ = NO_2
(III); R = R′ = NH_2



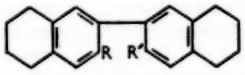
(IV)

Unsuccessful attempts to synthesise the dibenzodiphenylene (I) have been summarised by Bell and Hunter; [4] theoretical calculations have been made by Crawford,[5] and by using L.C.A.O. methods, the bond lengths and light-absorption data were predicted. We have briefly reported [6] the synthesis of 2 : 3-6 : 7-dibenzodiphenylene (I), and several other derivatives of diphenylene have been synthesised by similar methods; *e.g.*, 1 : 2-benzodiphenylene and 1 : 2-7 : 8-dibenzodiphenylene.[7] The latter compound exhibits considerable *cyclo*butadienoid character.

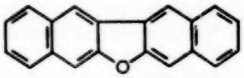
In the work now described 2 : 3-6 : 7-dibenzodiphenylene (I) has been synthesised from



(V)



(VI); R = R′ = NO_2
(VII); R = R′ = NH_2



(VIII)

3-nitro-2-naphthylamine, which was converted into 2-iodo-3-nitronaphthalene and thence into the hydrocarbon (I) by the series of reactions (II) ⟶ (III) ⟶ (IV) ⟶ (I).

3-Nitro-2-naphthylamine has been synthesised by van Rij, Verkade, and Wepster [8]

[1] Baker, Boarland, and McOmie, *J.*, 1954, 1476 (contains earlier references).
[2] Rosenhauer, Braun, Pummerer, and Reigelbauer, *Ber.*, 1937, **70**, 2281.
[3] Pummerer, Lüttringhaus, Fick, Pfaff, Riegelbauer, and Rosenhauer, *ibid.*, 1938, **71**, 2569.
[4] Bell and Hunter, *J.*, 1950, 2904.
[5] Crawford, *Canad. J. Chem.*, 1952, **30**, 47.
[6] Curtis and Viswanath, *Chem. and Ind.*, 1954, 1174, 1397.
[7] Cava and Stucker, *J. Amer. Chem. Soc.*, 1955, **77**, 6022.
[8] van Rij, Verkade, and Wepster, *Rec. Trav. chim.*, 1951, **70**, 236.

and by Ward [9] in low yield from 6-acetyl-1 : 2 : 3 : 4-tetrahydronaphthalene but preparation from 2-acetamidonaphthalene is simpler. High-pressure hydrogenation [10,11] over Raney nickel (W2) [12] gave 6-acetamido-1 : 2 : 3 : 4-tetrahydronaphthalene; this was nitrated by Schroeter's method [13] to the 7-nitro-compound which with *N*-bromosuccinimide gave a dibromo-derivative. This could not be dehydrobrominated directly, but treatment with methanolic potassium acetate produced a monobromo-derivative. Acid hydrolysis then gave 3-nitro-2-naphthylamine. This dehydrogenation [14] with *N*-bromosuccinimide is not of general application to substituted tetrahydronaphthalenes since it failed with the free amine and the corresponding iodo-compound.

3-Nitro-2-naphthylamine was diazotised and converted into 2-iodo-3-nitronaphthalene [15] which under Ullmann conditions gave 3 : 3'-dinitro-2 : 2'-dinaphthyl (II) but the m. p. did not agree with that recorded for the same compound by Cumming and Howie.[15]

FIG. 1. *Ultraviolet spectra in ethanol solution.* A, 2 : 3-6 : 7-*Dibenzodiphenylene* (I). B, 1 : 2-*Benzodiphenylene.* C, 1 : 2-7 : 8-*Dibenzodiphenylene.*

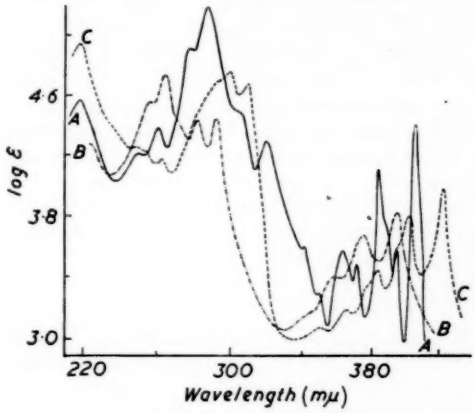
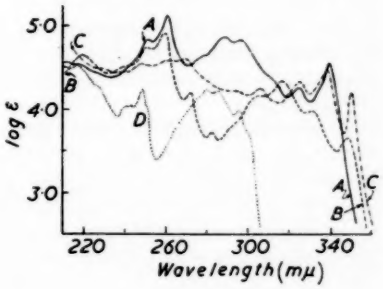


FIG. 2. *Ultraviolet spectra in ethanol solution.* A, *Dinaphtho*(2' : 3'-2 : 3)(2'' : 3''-4 : 5)-*furan* (VIII). B, *Brazan.* C, *Dinaphtho*(1' : 2'-2 : 3)(1'' : 2''-4 : 5)*furan.* D, *Diphenylene oxide.*



Previous attempts to reduce this type of dinitrodinaphthyl chemically have often been unsuccessful,[4,15,16] but catalytic hydrogenation gave 3 : 3'-diamino-2 : 2'-dinaphthyl (III) in good yield. Tetrazotisation and treatment with potassium iodide gave an iodonium iodide (not isolated) which was pyrolysed with cuprous oxide, under vacuum, giving 2 : 3-6 : 7-dibenzodiphenylene (I). The compound has an unusually high m. p. and great stability compared with 1 : 2-benzo- and 1 : 2-7 : 8-dibenzo-diphenylene; it is comparable with tetracene [17] in this respect. Reduction by freshly prepared Raney nickel in ethanolic solution gave 2 : 2'-dinaphthyl.

The ultraviolet absorption spectrum of 2 : 3-6 : 7-dibenzodiphenylene (Fig. 1) is complex and exhibits nine major and four minor maxima, being similar in this respect to 1 : 2-benzodiphenylene and 1 : 2-7 : 8-dibenzodiphenylene [7] and, although showing the expected bathochromic shift, similar in general form to that of diphenylene.[1] Maxima are recorded in Table 1: there is fair agreement with those predicted by Crawford.[5]

The infrared spectrum is relatively simple and shows several features of interest,

[9] Ward and Coulson, *J.*, 1954, 4545.
[10] B.P. 276,571.
[11] Casella and Co., G.P. 479,401; *Chem. Zentr.*, 1929, II, 3186.
[12] *Org. Synth.*, 1955, Coll. Vol. III, p. 181.
[13] Schroeter, *Annalen*, 1922, **426**, 65.
[14] Barnes, *J. Amer. Chem. Soc.*, 1948, **70**, 145.
[15] Cumming and Howie, *J.*, 1931, 3176.
[16] Huisberg and Sorge, *Annalen*, 1950, **566**, 162.
[17] Clar, "Aromatische Kohlenwasserstoffe," Springer-Verlag, Berlin, 1952, Vol. II, p. 232.

especially in relation to that of 1 : 2-benzo*cyclo*butene.[18] It has been pointed out [18] that, whereas xylene and tetralin both show a single intense band at 13·5 μ characteristic of *ortho*-disubstituted benzenes,[19] yet indane (a more strained molecule) exhibits two bands slightly separated at 13·30 and 13·55 μ. 4 : 5-Benzindane shows similar separation, with peaks at 13·10 and 13·57 μ.[20] 2 : 3-6 : 7-Dibenzodiphenylene possesses a very strong absorption at 13·45 μ and a partially separated double peak of medium intensity at 13·20 and 13·28 μ. All the other maxima show good correlation with the values suggested for substituted naphthalene derivatives by Hawkins, Ward, and Whiffen.[21]

For comparison we have recorded the infrared spectrum of diphenylene. This also exhibits the split peak at 13·34 and 13·63 μ, the latter being a very strong absorption. There does not appear to be any characteristic absorption by these two hydrocarbons which corresponds to the stretching of the four-membered ring. This may be due to the essential symmetry of the molecules.

The reduction of 3 : 3′-dinitro-2 : 2′-dinaphthyl (II) was difficult to control. With catalysts of high activity or at higher temperatures two other products were obtained in different experiments. On hydrogenation at 100° a compound $C_{20}H_{21}N$ probably 1′ : 2′ : 3′ : 4′ : 1″ : 2″ : 3″ : 4″-octahydro-2 : 3-6 : 7-dibenzocarbazole (V), was produced Comparison of the ultraviolet spectrum with that of carbazole [22] showed a similarity which would not be expected if the hydrogenated rings were adjacent to the pyrrole nucleus, since such a compound should show predominantly benzenoid absorption. In the infrared spectrum the NH stretching, NH deformation, and CN stretching frequencies occur at 2·94, 6·78, and 7·57 μ respectively (cf. carbazole, under the same conditions, 2·93, 6·69, and 7·54 μ).

Additional evidence that the outer rings in (V) were hydrogenated is that hydrogenation of 3 : 3′-dinitro-2 : 2′-dinaphthyl (II) with active catalysts at room temperature gave the diaminodinaphthyl (VII), also prepared by reduction of 5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-octahydro-3 : 3′-dinitro-2 : 2′-dinaphthyl (VI)

An attempt was made to prepare 1′ : 2′ : 3′ : 4′ : 1″ : 2″ : 3″ : 4″-octahydro-2 : 3-6 : 7-dibenzodiphenylene from 6-acetamido-1 : 2 : 3 : 4-tetrahydro-7-nitronaphthalene.[13] This was hydrolysed to the amine [13] and then converted into 1 : 2 : 3 : 4-tetrahydro-6-iodonaphthalene as described by Cumming and Howie.[15] Ullmann condensation gave 5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-octahydro-3 : 3′-dinitro-2 : 2′-dinaphthyl (VI) [15] and catalytic hydrogenation furnished the 3 : 3′-diamino-compound (VII), which was converted into the iodonium iodide and pyrolysed with cuprous oxide. In several experiments the fully aromatic 2 : 3-6 : 7-dibenzodiphenylene was obtained, but results depended very much upon unknown factors connected with the cuprous oxide (cf. Cava and Stucker [7]), since 2 : 2′-dinaphthyl was sometimes isolated as the sole product. This has been confirmed by Ward [23] who has, however, isolated the octahydrodibenzodiphenylene in one experiment.

A product of other experiments was considered, on comparison [24-26] of its ultraviolet absorption spectrum (Fig. 2), to be dinaphtho(2′ : 3′-2 : 3)(2″ : 3″-4 : 5)furan (VIII). This structure was supported by the infrared spectrum which was more complex than that of 2 : 3-6 : 7-dibenzodiphenylene and possessed a sharp peak at 9·35 μ (cf. peak at 9·49 μ in brazan [27] and 9·5 μ in 4 : 5-benzocoumaran [28]) which probably represents the antisymmetric

[18] Cava and Napier, *J. Amer. Chem. Soc.*, 1958, **80**, 2255.
[19] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen and Co., London, 1958, p. 77.
[20] Dannenberg and Rahman, *Ber.*, 1955, **88**, 1405.
[21] Hawkins, Ward, and Whiffen, *Spectrochim. Acta*, 1957, **10**, 105.
[22] Friedel and Orchin, " Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons Inc., N.Y., 1951, no. 338.
[23] Ward and Pearson, personal communication.
[24] Friedel and Orchin, *op. cit.*, no. 337.
[25] *Idem*, *op. cit.*, no. 435.
[26] *Idem*, *op. cit.*, no. 540.
[27] Chatterjee, *J. Indian Chem. Soc.*, 1956, **33**, 447.
[28] Cagniant and Cagniant, *Bull. Soc. chim. France*, 1955, 931.

ether C–O–C frequency for the five-membered ring.[29,30] The origin of the oxygen function is interesting, but Tauber and Halberstadt [31] have recorded the formation of diphenylene oxide from the tetrazonium salt of 2 : 2′-diaminodiphenyl by boiling with water.

TABLE 1. *Ultraviolet absorption spectra.* (*All in ethanol solution*; *wavelengths recorded in* mμ.)

(I) $\lambda_{max.}$	217	250	257	278	288	301	322	341	349	362	370	380	394	406
$\log \varepsilon_{max.}$	4·56	4·23	4·41	4·93	5·23	4·47	4·31	3·61	3·56	3·63	3·57	4·15	3·63	4·43
(VIII) $\lambda_{max.}$	212	252	261	278	288	297	324	340	360	370	380	394	406	
$\log \varepsilon_{max.}$	4·61	4·89	5·19	4·62	4·86	4·85	4·26	4·55	3·18	3·07	3·61	3·21	3·81	
(V) $\lambda_{max.}$	222	235	242	252	270	288	300	310	336					
$\log \varepsilon_{max.}$	4·54	4·55	4·54	4·39	4·45	4·31	4·40	4·33	3·90					

EXPERIMENTAL

*6-Acetamido-*1 : 2 : 3 : *4-tetrahydronaphthalene.*—To 2-acetamidonaphthalene (150 g.) suspended in decalin (distilled from Raney nickel) (250 ml.), Raney nickel (W2, 15 g.) in decalin suspension was added. The mixture was hydrogenated, with shaking, at 800 lb./sq. in. Reaction commenced at *ca.* 175° and was complete in 30 min. at 200°. This process was repeated with more (150 g.) material and the combined products were filtered (Filter-cel) and steam-distilled to remove decalin.

The residue, hydrochloric acid (*d* 1·2; 200 ml.), and ethanol (50 ml.) were boiled for 12 hr., cooled, and made alkaline with aqueous sodium hydroxide (25% w/v). After further cooling an oily layer separated and was collected. The aqueous layer was extracted with ether (2 × 100 ml.), which was combined with the oil, and dried ($MgSO_4$).

Distillation (14″ Vigreux column) gave a fore-run, b. p. up to 148°/19 mm. (14·0 g.), and 6-amino-1 : 2 : 3 : 4-tetrahydronaphthalene (165 g., 69%), b. p. 148—156°/19 mm., m. p. 38°. Schroeter [13] gives m. p. 38—39°. Acetylation gave 6-acetamido-1 : 2 : 3 : 4-tetrahydronaphthalene, m. p. 106° (from aqueous ethanol), in quantitative yield. Ward [9] gives m. p. 106°.

*6-Acetamido-*1 : 2 : 3 : 4-*tetrahydro-7-nitronaphthalene.*—The preceding compound was nitrated as described by Schroeter.[13] Satisfactory yields were obtained on the 75 g. scale provided that adequate cooling was maintained after the initial induction of nitration. Nitration at 40—42° gave optimum yields, and 6-acetamido-1 : 2 : 3 : 4-tetrahydro-7-nitronaphthalene was obtained as dark yellow needles (from ethanol), m. p. 134—135° (Verkade [8] gives m. p. 134—135°).

*6-Acetamido-*x : y-*dibromo-*1 : 2 : 3 : 4-*tetrahydro-7-nitronaphthalene.*—The acetamide (20 g.), *N*-bromosuccinimide (30·4 g., 2 mol.), and benzoyl peroxide (0·5 g.) in carbon tetrachloride (200 ml.) were heated under reflux over a 250-w infrared lamp, the lamp and flask being enclosed with aluminium foil. After the initial vigorous reaction, the solution was heated for a further 20 min. (longer heating resulted in lower yield). The red mixture was filtered hot and then concentrated (to *ca.* 100 ml.) in a current of nitrogen. After 1 hr. at 0°, *6-acetamido-*x : y-*dibromo-*1 : 2 : 3 : 4-*tetrahydro-7-nitronaphthalene* was collected as thin yellow needles (26·6 g., 81%), m. p. 134° (after crystallisation from carbon tetrachloride) (Found: C, 36·5; H, 3·3; Br, 37·0. $C_{12}H_{12}O_3N_2Br_2$ requires C, 36·75; H, 3·1; Br, 40·8%).

*6-Acetamido-*x-*bromo-*x : y-*dihydro-7-nitronaphthalene.*—The dibromo-compound (16·2 g.) was added rapidly to a boiling solution of potassium acetate (15 g.; fused) in dry methanol (150 ml.), and the solution boiled for 5 min. Potassium bromide separated and the product was then poured into water and chopped ice (2 l.). After 12 hr. at 0° the very pale yellow solid was collected (13·2 g., quantitative yield), m. p. 154—156° (decomp.). One crystallisation from methanol gave the *monobromo-compound* as pale cream needles, m. p. (rapid heating) 172° (decomp.) (Found: C, 45·55; H, 3·4; Br, 22·1. $C_{12}H_{11}O_3N_2Br$ requires C, 46·3; H, 3·6; Br, 25·7%). Both mono- and di-bromides were difficult to analyse for bromine.

3-Nitro-2-naphthylamine.—The monobromo-compound (13·0 g.), ethanol (100 ml.), hydrochloric acid (*d* 1·2, 50 ml.), and water (10 ml.) were boiled for 1 hr. and then poured into excess of dilute aqueous ammonia. After the mixture had been kept at 0° overnight, the precipitate

[29] Bellamy, *op. cit.*, p. 114.
[30] Barrow and Searles, *J. Amer. Chem. Soc.*, 1953, **75**, 1175.
[31] Tauber and Halberstadt, *Ber.*, 1892, **25**, 2745.

was collected and dried (6·53 g., 83%). One crystallisation from light petroleum (b. p. 60—80°) gave 3-nitro-2-naphthylamine as deep red needles, m. p. 115—116°. Ward [9] gives m. p. 115—116° (Found: C, 63·7; H, 3·9; N, 14·9. Calc. for $C_{10}H_8O_2N_2$: C, 63·8; H, 4·3; N, 14·9%).

2-Iodo-3-nitronaphthalene.—Sodium nitrite (4·7 g.) in sulphuric acid (*d* 1·84; 30 ml.) at 0° was heated to 70° and then cooled to 10°. This solution was used to diazotise 3-nitro-2-naphthylamine (12·8 g.) in acetic acid (150 ml.) and sulphuric acid (*d* 1·84; 2 ml.) by dropwise addition below 20°. The solution was stored for 30 min. at room temperature and then poured into potassium iodide (30 g.) in water (80 ml.). After 24 hr. at 0°, the solid was collected, dried, dissolved in benzene, and passed through alumina (acid washed, activated at 110° for 12 hr.). Evaporation of the eluate and crystallisation from aqueous ethanol gave 2-iodo-3-nitronaphthalene as deep yellow needles (8·5 g., 47%), m. p. 89—90°. Cumming and Howie [15] give m. p. 89° (Found: C, 40·6; H, 2·0; I, 42·2. Calc. for $C_{10}H_6O_2NI$: C, 40·2; H, 2·0; I, 42·4%).

3 : 3′-Dinitro-2 : 2′-dinaphthyl (II).—2-Iodo-3-nitronaphthalene (1·97 g.) was heated with copper-bronze powder (5·0 g.) in a wide test-tube immersed in an oil-bath at 130—135° for 40 min. Stirring was maintained and a few crystals of iodine were added occasionally. The product was extracted with hot benzene (3 × 100 ml.), and the extract concentrated (to *ca.* 10 ml.) before being passed through alumina. Evaporation of the eluate gave 3 : 3′-dinitro-2 : 2′-dinaphthyl (II) as yellow needles (0·35 g.), m. p. 270—271°. Recrystallisation from benzene gave m. p. 275° (Found: C, 69·7; H, 3·4. Calc. for $C_{20}H_{12}O_4N_2$: C, 69·8; H, 3·5%). Cumming and Howie record m. p. 257°.

3 : 3′-Diamino-2 : 2′-dinaphthyl (III).—The dinitro-compound (II) (1·36 g.) suspended in ethanol (50 ml.) and acetic acid (10 ml.) was shaken with Raney nickel (W2, which had been kept under ethanol for 2 weeks; *ca.* 3 g.) under hydrogen at 40 lb./sq. in. in a glass bottle until the solution was colourless (approx. 2 hr.). The product was filtered (Filter-cel), diluted with water (200 ml.), saturated with hydrogen, and kept at 0° for 24 hr. The precipitate was collected and crystallised from ethanol (charcoal), giving *3 : 3′-diamino-2 : 2′-dinaphthyl* as needles (0·75 g., 67%), m. p. 215—220°. Recrystallisation gave m. p. 220° (decomp.), darkening rapidly in air. The *diacetyl* derivative, long, stout, needles from acetic acid, had m. p. 164—165° (Found: C, 77·9; H, 5·4; N, 7·2. $C_{24}H_{20}O_2N_2$ requires C, 78·2; H, 5·5; N, 7·6%).

2 : 3-6 : 7-Dibenzodiphenylene (I).—The diamine (III) (0·70 g.) in 6N-hydrochloric acid (15 ml.) was treated dropwise with a solution of sodium nitrite (0·51 g.) in water (1 ml.) with rapid stirring at 5°. The mixture was stirred for 30 min., and then treated with potassium iodide (2 g.) in water (5 ml.). Nitrogen was rapidly evolved and a dark brown amorphous solid separated. The mixture was set aside for 30 min., saturated sodium sulphite solution (10 ml.) added, and the solid collected. This was washed with sodium sulphite solution, then cold methanol (7 ml.), and dried, giving the iodonium iodide as a brown powder (1·03 g.).

This powder (350 mg.) was intimately mixed with cuprous oxide (3·5 g.) and pyrolysed under partial vacuum (*ca.* 30 mm.) in a cold-finger sublimation apparatus immersed in a metal-bath at 350°; a yellow semi-solid rapidly sublimed. This process was repeated on two further portions, and the combined solid was collected in hot benzene (20 ml.), filtered (charcoal), and concentrated (to *ca.* 2 ml.). The crystalline solid was collected and sublimed three times at 390°/10 mm. (bath temp.), giving *2 : 3-6 : 7-dibenzodiphenylene* (I) as thin, twinned, rectangular plates (15 mg., approx. 3%), m. p. (sealed tube) 376° ± 2° (corr.). Crystallisation from benzene gave discrete, very pale yellow plates (Found: C, 95·3, 95·1; H, 4·9, 5·0. $C_{20}H_{12}$ requires C, 95·2; H, 4·8%). (The molecular weight could not be determined by the Kofler technique since the compound was insoluble in the usual solvents.) The hydrocarbon sublimes rapidly without melting at 340—345° on the Kofler block. Its dilute solution in benzene exhibits a strong blue fluorescence.

The infrared spectrum was determined in a potassium bromide disc; the maxima (μ) were: 6·05 (w), 6·20 (w), 6·66 (w), 6·89 (w), 7·91 (w), 8·07 (w), 8·51 (w), 8·78 (w), 8·84 (w), 9·76 (w), 10·50 (m), 11·39 (v.s.), 13·2 (m), 13·28 (m), 13·45 (s). The infrared spectrum of diphenylene under the same conditions showed maxima at 6·94 (m), 7·06 (m), 7·50 (w), 7·96 (m), 8·58 (w), 8·70 (m), 8·85 (m), 9·02 (w), 10·44 (s), 10·86 (m), 11·29 (m), 12·63 (w), 13·34 (m), 13·52 (s), 13·63 (s) μ.

Reduction of 2 : 3-6 : 7-*Dibenzodiphenylene* (I).—2 : 3-6 : 7-Dibenzodiphenylene (26·5 mg.) in ethanol (35 ml.) at 50° was shaken with freshly prepared Raney nickel (*ca.* 1 g.) for 5 min., the faint blue fluorescence then having disappeared. The filtered solution was concentrated (to 10 ml.) and on cooling yielded plates, m. p. 180—183°. Sublimation at 150°/13 mm. and

crystallisation from ethanol gave 2 : 2′-dinaphthyl (8 mg.), m. p. 184° undepressed when mixed with authentic material, and showing an identical infrared curve.

Anomalous Reductions of 3 : 3′-*Dinitro*-2 : 2′-*dinaphthyl* (II).—(*a*) The dinitro-compound (II) (0·3 g.) in ethanol (20 ml.) and acetic acid (5 ml.) was hydrogenated over Raney nickel under hydrogen (150 lb./sq. in.) at 110° for 1 hr. The solution was cooled and filtered, and on addition of water (200 ml.) yielded a pale green solid. This was collected, dried, and recrystallised from benzene (intensely fluorescent solution) to give 1′ : 2′ : 3′ : 4′ : 1″ : 2″ : 3″ : 4″-*octahydro*-2 : 3-6 : 7-*dibenzocarbazole* (V) as pale green-yellow plates (0·08 g.), m. p. 275° (Found: C, 87·5; H, 7·2; N, 5·2. $C_{20}H_{21}N$ requires C, 87·2; H, 7·7; N, 5·1%). The infrared spectrum in potassium bromide showed maxima (μ) at 2·94 (s), 3·32 (w), 3·41 (s), 3·50 (m), 6·16 (m), 6·78 (s), 6·93 (m), 7·12 (w), 7·47 (m), 7·78 (w), 8·06 (s), 8·59 (w), 8·82 (w), 9·28 (w), 10·42 (w), 10·55 (w), 10·97 (m), 11·75 (s), 12·28 (w), 13·35 (m), 13·47 (m).

(*b*) The dinitro-compound (II) (4·0 g.) suspended in ethanol (150 ml.) and acetic acid (30 ml.) was shaken with freshly prepared Raney nickel (W2; *ca.* 4 g.) under hydrogen at 40 lb./sq. in. until colourless. The solution was filtered, diluted with water (500 ml.), and kept under hydrogen for 24 hr. at 0°. The precipitate was collected and dried. Recrystallisation from benzene (charcoal) gave 3 : 3′-*diamino*-5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-*octahydro*-2 : 2′-*dinaphthyl* as prisms (2·1 g.), m. p. 191—192° (Found: C, 82·1; H, 8·3; N, 9·6. $C_{20}H_{24}N_2$ requires C, 82·15; H, 8·3; N, 9·6%).

6-*Amino*-1 : 2 : 3 : 4-*tetrahydro*-7-*nitronaphthalene*.—This compound was prepared by acid hydrolysis of the acetamido-compound substantially as described by Ward [9]; it had m. p. 125—127°.

1 : 2 : 3 : 4-*Tetrahydro*-6-*iodo*-7-*nitronaphthalene*.—Sodium nitrite (10 g.) in sulphuric acid (*d* 1·84; 70 ml.) was heated to 70° and then cooled to 10°. This solution was used to diazotise the foregoing amine (25·4 g.) in acetic acid (300 ml.) and sulphuric acid (*d* 1·84; 3 ml.), at 10—15°. After 30 min. the solution was added to potassium iodide (60 g.) in water (100 ml.) and vigorously stirred. After 24 hr. at 0°, the solid was collected, washed with aqueous sodium sulphite, and crystallised from ethanol, forming pale orange needles (19·0 g., 47%), m. p. 76°. Cumming and Howie [15] give m. p. 76° for this compound prepared in very low yield.

5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-*Octahydro*-3 : 3′-*dinitro*-2 : 2′-*dinaphthyl* (VI).—This compound was prepared as described by Cumming and Howie [15] from the foregoing iodo-compound by using copper powder. Control of temperature at 110—120° to avoid violent decomposition was important, but even in these circumstances it was difficult to obtain a yield as high as that claimed.[15] After purification by chromatography over alumina, the m. p. of the product could not be raised to that stated (201°).[15] Recrystallisation from acetic acid gave yellow needles, m. p. 192° (Found: C, 68·1; H, 5·3; N, 8·5. Calc. for $C_{20}H_{20}O_4N_2$: C, 68·2; H, 5·7; N, 7·95%).

3 : 3′-*Diamino*-5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-*octahydro*-2 : 2′-*dinaphthyl* (VII).—The dinitro-compound (XV) (0·5 g.) in ethanol (25 ml.) and acetic acid (2·5 ml.) was reduced over Raney nickel (W2, *ca.* 0·5 g.) as described above for (III). When worked up in the usual way, the diamine was obtained as microcrystalline prisms (from benzene) (0·35 g.), m. p. (and mixed m. p. with material prepared as above) 192°.

2 : 3-6 : 7-*Dibenzodiphenylene from* 3 : 3′-*Diamino*-5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-*octahydro*-2 : 2′-*dinaphthyl* (VII).—The diamine (1·6 g.) in hydrochloric acid (*d* 1·2; 17 ml.) and water (17 ml.) was treated with sodium nitrite (1·2 g.) in water (3 ml.) at 5°, with vigorous stirring. After 30 min., the solution was poured into potassium iodide (5 g.) in water (10 ml.). The solid was collected, washed with aqueous sodium sulphite and ice-cold methanol (2 ml.), and dried (2·1 g.).

Pyrolysis of this salt (0·35 g.) with cuprous oxide (3·5 g.) (Baker's " Analysed " grade) under the same conditions as for 2 : 3-6 : 7-dibenzodiphenylene gave a product which was combined with those from four similar runs. The combined material gave 2 : 3-6 : 7-dibenzodiphenylene from benzene as pale yellow plates (0·26 g.), m. p. (sealed tube) 357° (uncorr.), showing no depression with the sample prepared from the fully aromatic precursor.

Anomalous Pyrolysis of 3 : 3′-*Diamino*-5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 9′-*octahydro*-2 : 2′-*dinaphthyl* (VII).—*Dinaphtho*(2′ : 3′-2 : 3)(2″ : 3″-4 : 5)*furan* (VIII). The diamine (VII) (1·45 g.) was tetrazotised in the usual way, giving the iodonium iodide (2·45 g.). This was pyrolysed, in seven portions (0·35 g.), with cuprous oxide (3·5 g.), exactly as described above. The combined products yielded the *dinaphthofuran* (VIII) from benzene as pale yellow plates (70 mg.), m. p. 260°. Recrystallisation gave m. p. 266° (subliming at the m. p.) [Found: C, 88·7, 89·7; H,

4·55, 4·3%; *M* (Rast), 272. $C_{20}H_{12}O$ requires C, 89·5; H, 4·5%; *M*, 268]. Its 2 : 4 : 7-*trinitrofluorenone complex* (prepared in benzene solution) formed deep purple-brown needles (from benzene), m. p. 244—246° (decomp.) (Found: C, 68·4; H, 3·0; N, 6·9. $C_{20}H_{12}O,C_{13}H_5O_7N_3$ requires C, 67·9; H, 2·9; N, 7·2%).

The infrared spectrum of the furan in potassium bromide showed maxima (μ) at 6·18 (w), 6·28 (w), 6·69 (w), 6·84 (w), 7·24 (w), 7·50 (m), 7·86 (w), 8·29 (w), 8·39 (m), 8·81 (w), 9·35 (m-s), 9·69 (w), 9·85 (w), 10·45 (m), 11·41 (v.s.), 11·85 (w), 13·04 (w), 13·32 (m-s), 13·54 (vs).

Microanalyses were by Mr. J. Walter, the Johns Hopkins University, and Dr. F. Pascher, Mikroanalytische Laboratorium, Bonn. Infrared spectra were determined by Dr. Lester Kuhn, Aberdeen Proving Grounds, Aberdeen, Maryland, U.S.A., and by Mr. D. Jones of this Department (Swansea). We thank Dr. H. E. Hallam for advice on infrared spectra; one of us (G. V.) thanks Andhra University, Waltair, India, for study leave.

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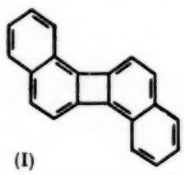
332. *The Synthesis of* 2 : 3-6 : 7-*Dibenzodiphenylene, and a Note on the Reaction of* 1-*Bromo*-2-*iodonaphthalene with Magnesium.*

By E. R. Ward and B. D. Pearson.

2 : 3-6 : 7-Dibenzodiphenylene has been synthesised by the pyrolysis of 5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-octahydro-2 : 2′-dinaphthyl-3 : 3′-iodonium iodide and is accompanied by two other products which appear to be hydrogenated derivatives of the dibenzodiphenylene. The pyrolysis of the corresponding 3 : 3′-tetrazonium sulphate has also been studied.

Four dibenzodiphenylenes are possible; the 1 : 2-5 : 6- (I), 1 : 2-6 : 7-, 1 : 2-7 : 8- and 2 : 3-6 : 7-isomers (II). Brief details of the synthesis of the last were given by Curtis and Viswanath [1] in 1954 and the synthesis of the third was described fully by Cava and Stucker [2] in 1955. As a first step in a study of the preparation and properties of dibenzodiphenylenes, we investigated the synthesis of the 2 : 3-6 : 7-isomer (II), since the third does not appear to be very stable. Our independent synthesis followed the second route described fully by Curtis and Viswanath,[3] and our results obtained closely parallel theirs, although at some stages our yields were higher. Thus, contrary to our previous experience [4] we were able, by using a new procedure, satisfactorily to nitrate 6-acetamido-1 : 2 : 3 : 4-tetrahydronaphthalene in reasonably large amounts and our yields were appreciably greater than those of Schroeter.[5] Like Curtis and Viswanath,[3] in the final pyrolysis of



(I)

(II)

5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-octahydro-2 : 2′-dinaphthyl-3 : 3′-iodonium iodide with cuprous oxide, we obtained varying results for which we could not account but which seemed to depend on the activity of the oxide used (cf. Cava and Stucker [2]). Our pyrolyses were carried out in nitrogen under reduced pressure, and in one experiment we obtained the

[1] Curtis and Viswanath, *Chem. and Ind.*, 1954, 1174, 1397.
[2] Cava and Stucker, *J. Amer. Chem. Soc.*, 1955, **77**, 6022.
[3] Curtis and Viswanath, preceding paper.
[4] Ward and Coulson, *J.*, 1954, 4545.
[5] Schroeter, *Annalen*, 1922, **426**, 1.

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dibenzodiphenylene (II) in 4·5% yield, together with another yellow substance (*A*), m. p. 224—226°. However, in another experiment we obtained very thin pale yellow plates (*B*), m. p. 300—302°, together with more of (*A*). Like the dibenzodiphenylene (II), (*B*) but not (*A*) displayed, in dilute benzene, a strong blue fluorescence which disappeared on concentration. The ultraviolet spectra suggest that both (*A*) and (*B*) contain the 2 : 3-6 : 7-dibenzodiphenylene skeleton; (*A*) may be an octahydro-compound and (*B*) a tetrahydrodibenzodiphenylene. Further attempts to prepare the dibenzodiphenylene (II) by reaction of magnesium with 2-bromo-3-iodonaphthalene (see below) or by the pyrolysis of 5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-octahydro-2 : 2′-dinaphthyl-3 : 3′-tetrazonium sulphate with cuprous oxide at red heat, under a reduced pressure of nitrogen, failed. In the latter experiment two apparently pure crystalline products were obtained: one possibly 2 : 3-6 : 7-dibenzocarbazole (ultraviolet spectra; analysis), the other an octahydrodibenzocarbazole, though not identical with the octahydrodibenzocarbazole reported by Curtis and Viswanath.[3]

FIG. 1. FIG. 2.

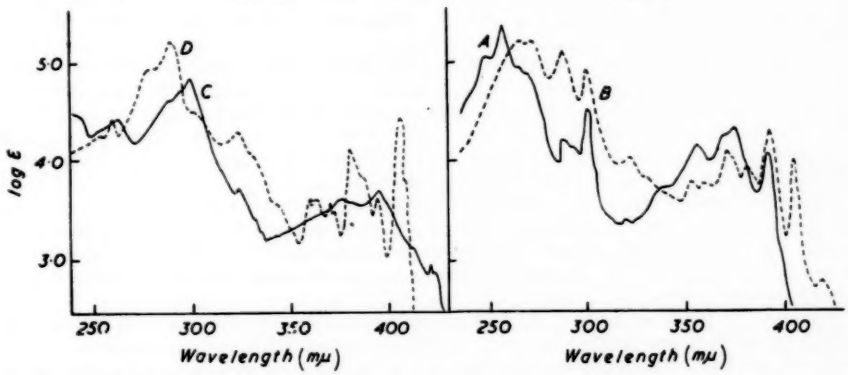

FIG. 1. *Ultraviolet spectra of* 2 : 3-6 : 7-*dibenzodiphenylene* (II) (D) *and substance* (C), *possibly* 1 : 2-5 : 6-*dibenzodiphenylene* [$\lambda_{max.}$ in mμ (log ε) 261 (4·37), 297 (4·82), 324 (3·66), 375 (3·62), 381 (3·59), 394 (3·71), 420 (2·93); $\lambda_{min.}$ 248 (4·23), 271 (4·16), 321 (3·63), 337 (3·17), 379 (2·57), 383 (3·55), 419 (2·80); λ_{sh} 241 (4·45), 288 (4·62), 293 (4·68), 340 (3·20), 411 (3·10), 423 (2·84)].

FIG. 2. *Ultraviolet spectra of substances* (A) *and* (B) *obtained by pyrolysis of* 5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-*octahydro*-2 : 2′-*dinaphthyl*-3 : 3′-*iodonium iodide*: *Substance* (A) $\lambda_{max.}$ (mμ) 249, 258, 266, 288, 295, 300, 319, 339, 356, 375, 393; $\lambda_{min.}$ 253, 264, 286, 292, 297, 316, 324, 342, 363, 386.
Substance (B) $\lambda_{max.}$ 265, 272, 287, 300, 322, 353, 359, 371, 381, 393, 406, 419; $\lambda_{min.}$ 270, 281, 296, 316, 348, 356, 364, 378, 387, 401, 416.
Other spectra recorded, but not illustrated are:
(*a*) 3 : 3-Dinitro-5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-octahydro-2 : 2′-dinaphthyl: $\lambda_{max.}$ 280 (4·15), $\lambda_{min.}$ 256 (4·12) λ_{sh} 352 (3·35), 378 (2·82).
(*b*) 3 : 3′-Diamino-5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-octahydro-2 : 2′-dinaphthyl: $\lambda_{max.}$ 303 (3·81), $\lambda_{min.}$ 283 (3·69), λ_{sh} 348 (3·27).
(*c*) Products from pyrolysis of 5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-octahydro-2 : 2′-dinaphthyl-3 : 3′-tetrazonium sulphate.
(i) A dibenzocarbazole (?): $\lambda_{max.}$ 245, 254, 267, 273, 279, 290, 300, 314, 319, 334, 360, 378; $\lambda_{min.}$ 261, 286, 296, 305, 316, 323, 354, 372.
(ii) An octahydrodibenzocarbazole (?): $\lambda_{max.}$ (mμ) 248, 256, 266, 301, 306, 312, 335, 337, 342, 349; $\lambda_{min.}$ (mμ) 251, 262, 271, 304, 309, 332, 336, 240, 346.
All spectra were recorded by a Unicam S.P. 500 photoelectric spectrophotometer on ethanol solutions.

Heaney, Mann, and Millar[6] obtained diphenylene, in 3·5% yield, by reaction of magnesium (2·2 equiv.) with ethereal *o*-bromoiodobenzene. McOmie and his co-workers[7] have prepared substituted diphenylenes, in low yield, by a similar method. We were

[6] Heaney, Mann, and Millar, *J.*, 1957, 3930.
[7] McOmie, personal communication.

unable to make ethereal 2-bromo-3-iodonaphthalene react, but found that ethereal 1-bromo-2-iodonaphthalene would react with *ca.* 1 equiv. of magnesium. After carboxylation, a solid product was isolated, and fractional crystallisation of this gave 2 : 2′-dinaphthyl, a small amount of thin orange plates (*C*); but mainly a heavy viscous oil which could not be purified. The ultraviolet spectrum of material (*C*) suggests that it may be **1 : 2-5 : 6**-dibenzodiphenylene (I) as it strongly resembles the spectra of the **1 : 2-7 : 8**- and **2 : 3-6 : 7**-compounds. When this experiment was repeated on a double scale the yield of (*C*) was even smaller.

Experimental

1-Bromo-2-iodonaphthalene.—1-Bromo-2-naphthylamine (10 g.) was dissolved in warm sulphuric acid (*d* 1·84; 7 c.c.)–water (20 c.c.) and diazotised, at 0°, by rapid addition of sodium nitrite (5 g.) in water (15 c.c.). The diazonium solution was added to one of iodine (6 g.) and potassium iodide (18 g.) in water (120 c.c.) with stirring, and after 1 hr. the solids were collected. These were shaken with 10% w/v aqueous sodium thiosulphate (200 c.c.), collected again, washed with water, dried, and dissolved in benzene. The solution was filtered through alumina and allowed to crystallise; the product (6·0 g., 45%) had m. p. 94° (from benzene) (Meldola [8] gives m. p. 94°).

2-Bromo-3-iodonaphthalene.—3-Bromo-2-naphthylamine (10 g.) was dissolved in a solution of sodium nitrite (4 g.) in sulphuric acid (*d* 1·84; 40 c.c.), and the mixture stirred into acetic acid (80 c.c.) below 30°. After 1 hr. the diazonium solution was decomposed as above, and the product collected and washed as before, giving crude *2-bromo-3-iodonaphthalene* (10 g., 75%); m. p. 120° from ethanol–ethyl acetate (2 : 1 v/v) (Found: C, 36·0; H, 1·9; Halogen, 61·8. $C_{10}H_6BrI$ requires C, 36·0; H, 1·8; Halogen, 62·2%).

2-Iodo-3-nitronaphthalene.—A solution of 3-nitro-2-naphthylamine (10 g.) in acetic acid (120 c.c.) was slowly added, with stirring, to one of sodium nitrite (4 g.) in sulphuric acid (*d* 1·84; 40 c.c.) below 30°. Crude 2-iodo-3-nitronaphthalene (14 g., 88%), was obtained, by the procedure given for the preparation above, m. p. 89° (from ethanol). (Cumming and Howie [9] give m. p. 89°.)

Nitration of 6-Acetamido-1 : 2 : 3 : 4-tetrahydronaphthalene.—The amide [4] (50 g.) in acetic anhydride (810 c.c.) was treated dropwise (*ca.* 80 min.), with stirring, with a mixture of acetic anhydride (16·7 c.c.) and nitric acid (*d* 1·42; 16·7 c.c.), the temperature being kept below 25°. Next morning, the mixture was poured, with stirring, into ice–water (5 l.) which yielded a sticky product. Most of the liquid was siphoned off and replaced by warm water, and further stirring then gave a granular product (cf. Ward and Coulson [4]). This was collected, washed with water, dried, and crystallised from hot ethanol (*ca.* 170 c.c.), yielding almost pure 6-acetamido-1 : 2 : 3 : 4-tetrahydro-7-naphthalene (yields 35—39%). Further amounts were obtained (total yield *ca.* 42%) by evaporation of the ethanolic mother-liquor to dryness and separation from accompanying 5-nitro-isomer by chromatography on alumina in benzene–ethyl acetate (2 : 1 v/v).

1 : 2 : 3 : 4-Tetrahydro-6-iodo-7-nitronaphthalene.—This was prepared by diazotising [10,11] the above amine, and adding the diazonium solution to aqueous iodine–potassium iodide, underlaid with chloroform (cf. Kharasch, Kalfoyan, and Arterberry [12]), the product being obtained from the chloroform layer. Yields varied from 60 to 80% but the m. p. could not be raised to that given by Cumming and Howie,[9] *viz.*, 76°, despite repeated crystallisation. However, the compound behaved satisfactorily subsequently.

3 : 3′-Dinitro-5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-octahydro-2 : 2′-dinaphthyl.—The halogeno-compound (1 g.) was heated to 132° in a constant-temperature heater,[13] and copper-bronze (0·6 g.) added portionwise, with good stirring, during 30 min., the temperature being kept below 140°; and the heating was continued for a further 30 min. The product was extracted with hot benzene (3 × 50 c.c.) and chromatographed on alumina; the first orange band gave the required dinaphthyl, m. p. 190—191° (0·42 g., 73%). This material was used in the next stage but it

[8] Meldola, *J.*, 1885, 497.
[9] Cumming and Howie, *J.*, 1931, 3176.
[10] Hodgson and Walker, *J.*, 1933, 1620.
[11] Hodgson and Turner, *J.*, 1943, 86.
[12] Kharasch, Kalfoyan, and Arterberry, *J. Org. Chem.*, 1956, **21**, 925.
[13] Tucker, *J. Chem. Educ.*, 1953, **30**, 634.

could be purified by crystallisation from boiling ethanol–ethyl acetate (1 : 1 v/v), giving m. p. 197—198° (Cumming and Howie [9] give m. p. 201°).

3 : 3′-*Diamino*-5 : 6 : 7 : 8 : 5′ : 6′ : 7′ : 8′-*octahydro*-2 : 2′-*dinaphthyl*.—The nitro-product (3·5 g.) was dissolved in ethyl acetate (165 c.c.) and ethanol (15 c.c.) in the presence of B.D.H. stabilised Raney nickel (3 g.), and treated with hydrogen at *ca.* 75° and atmospheric pressure. After 8 hr. *ca.* 2 l. of hydrogen had been taken up and reduction appeared to be complete. After removal of catalyst the solution was concentrated to 60 c.c., yielding almost pure diamine (1·56 g.). More was obtained by evaporating the solution to dryness and extracting the residue with hydrochloric acid (*d* 1·2; 2 × 30 c.c.). The diamine (total yield 2·2 g., 76%) had m. p. 193—194°, from ethyl acetate–ethanol (1 : 1 v/v) (Found: C, 81·1; H, 8·1; N, 9·15. Calc. for $C_{20}H_{24}N_2$: C, 82·15; H, 8·3; N, 9·6%). Reduction at room temperature with hydrazine in the presence of Raney nickel or palladised charcoal was not successful.

Preparation and Pyrolysis of the 3 : 3′-*Iodonium Iodide*.—The diamine (0·15 g.) in hydrochloric acid (*d* 1·2; 1·5 c.c.)–water (2 c.c.) was treated at 0° with sodium nitrite (0·2 g.) in water (1 c.c.), and the diazonium solution decomposed by addition to iodine (0·3 g.) and potassium iodide (1 g.) in water (20 c.c.). After 1 hour's stirring, the solids were collected, dried, and extracted with benzene (200 c.c., Soxhlet). The residual iodonium iodide (0·24 g., 92%) was insoluble in boiling water or acetone, and decomposed at 240—245°. Diazotisation by Hodgson and Walker's method [10] and similar decomposition gave 83% yield. The benzene extract from either method was washed with aqueous sodium thiosulphate and water, dried, and chromatographed on alumina. After elution of a tarry band, further elution by benzene–ethyl acetate (1 : 2 v/v) gave green crystals (0·016 g.), m. p. 208° unchanged by further crystallisation from benzene.

An intimate mixture of the iodonium iodide (*ca.* 0·3 g.) and cuprous oxide (3 g.), in an atmosphere of nitrogen at 0·3 mm., was heated at 340° in a sand-bath for 30 min.; then the temperature allowed to fall to *ca.* 220° at which it was kept for 1 hr. The product was extracted with benzene (150 c.c.; Soxhlet) for 8 hr., and the solution concentrated to 20 c.c., very thin, pale yellow plates crystallising. The benzene mother-liquor was chromatographed on alumina, giving a yellow solid, which formed yellow needles from ethanol.

(*a*) When freshly prepared cuprous oxide was used, 0·288 g. of iodonium iodide afforded very thin yellow plates of (II), which sublimed at 344—346° without melting (5 mg., 4·5%). The ultraviolet spectrum of this was identical with that recorded by Curtis and Viswanath.[3] The yellow needles (*A*) (3 mg.) had m. p. 224—226°.

(*b*) With an old sample of cuprous oxide, 0·3 g. of iodonium iodide afforded very thin pale yellow plates (*B*), m. p. 300—302° (4 mg.; 2·6% calc. as a *tetrahydrodibenzodiphenylene*) (Found: C, 93·2; H, 6·0. $C_{20}H_{16}$ requires C, 93·8; H, 6·2%), and yellow needles, m. p. 224—226° (4 mg.).

Preparation and Pyrolysis of the 3 : 3′-*Tetrazonium Sulphate*.—The appropriate diamine (0·5 g.) was dissolved in a solution of sodium nitrite (0·4 g.) in sulphuric acid (*d* 1·84; 4 c.c.) and added with stirring to acetic acid (9 c.c.), below 30°. After 1 hour's stirring, ice-cold dry ether (100 c.c.) was added, and then after 1 hr. at room temperature the tetrazonium sulphate was collected, washed with acetic acid–ether (1 : 1 v/v), and then with ether alone, and dried under reduced pressure (*ca.* 0·8 g.). This was ground with cuprous oxide (7 g.), the mixture covered with more cuprous oxide (5 g.), and the whole pyrolysed at dull red heat, in nitrogen at 0·3 mm. After cooling *in vacuo*, the mixture was extracted by benzene (200 c.c.; Soxhlet); the extract on concentration to *ca.* 30 c.c. gave pale yellow crystals which, recrystallised from benzene, had m. p. 299—301° (subliming above 285°) (5 mg.) (Found: C, 89·9; H, 5·2. A *dibenzocarbazole*, $C_{20}H_{13}N$, requires C, 89·9; H, 4·9%). The mother-liquors were chromatographed on alumina giving, by elution with benzene, a solid (36 mg.), m. p. 157—158° (from ethanol) (Found: C, 86·9; H, 7·9. An *octahydrodibenzocarbazole*, $C_{20}H_{21}N$, requires C, 87·3; H, 7·6%). Further elution with ethyl acetate gave a yellow residue (3 mg.) not investigated further.

Interaction of 1-*Bromo*-2-*iodonaphthalene with Magnesium*.—1-Bromo-2-iodonaphthalene (11 g.) in ether (120 c.c.) was added during 30 min. to a stirred mixture of magnesium (1·75 g., 2·2 equiv.) and ether (50 c.c.), the reaction being initiated by addition of iodine and a trace of methylmagnesium iodide, and conducted under nitrogen. After 1 hour's refluxing, dry benzene (60 c.c.) was added at 0°, and refluxing continued for a further hour. Unchanged magnesium was removed, and carboxylation carried out by pouring on to a slurry of ether and solid carbon dioxide followed by acidification with 20% w/v hydrochloric acid (500 c.c.). Fractional

crystallisation from benzene of solids from the ether layer gave 2 : 2′-dinaphthyl (0·5 g.), some orange *plates* (12 mg.), m. p. 271° (Found: C, 92·0; H, 6·0. $C_{20}H_{12}$ requires C, 95·2; H, 4·8%), and a heavy viscous liquid which could not be distilled at 3 mm. The red *trinitrofluorenone* derivative of the plates had m. p. 267° (Found: C, 70·8; H, 5·2. $C_{33}H_{17}O_7N_3$ requires C, 69·9; H, 3·0%).

The authors are indebted to Dr. R. F. Curtis for information on the preparation of 3-nitro-2-naphthylamine and the properties of 2 : 3-6 : 7-dibenzodiphenylene, to Dr. J. F. W. McOmie for information on his work in the diphenylene field, and to the Department of Scientific and Industrial Research for a special grant.

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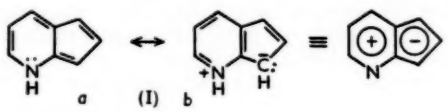
333. *Heterocyclic Analogues of Azulene.**

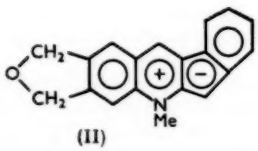
By M. Los and (the late) W. H. STAFFORD.

Some analogues of benzazulene are prepared containing nitrogen or oxygen in the central benzene ring. They are highly coloured and behave as anhydro-salts. Their properties and spectra are discussed.

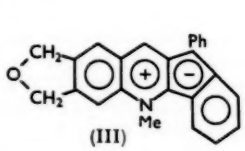
SINCE replacement of a CH=CH group in an aromatic system by NR, S, or O results in a molecule not unlike that of the parent compound, *cyclo*penta[*b*]pyridine (I) might be expected to resemble azulene. Armit and Robinson [1] prepared indenoquinolines (II)



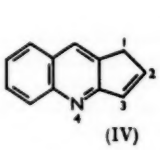
(I) a b



(II)



(III)



(IV)

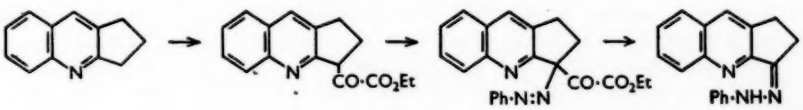
and (III) to prove that aromatic character may be associated with a five-membered ring. Although these compounds were highly coloured, their complexity prevents comparison with the azulenes, and so attempts were made to synthesise simpler analogues. Although neither *cyclo*penta[*b*]pyridine (I) nor its benzo-derivative, β-quinindene (IV), could be obtained, derivatives of the latter have been prepared. When Prelog and Szpilfogel [2] tried to dehydrogenate the dihydro-derivative of (I), only starting material was recovered. Borsche [3] synthesised 2 : 3-dihydro-β-quinindene from *cyclo*pentanone by the Pfitzinger reaction with subsequent decarboxylation of the 9-carboxylic acid so produced. Attempted dehydrogenation of methyl 2 : 3-dihydro-β-quinindene-9-carboxylate by sulphur gave only starting material. The dihydro-compound with *N*-bromosuccinimide gave a compound, presumably the 3-bromo-derivative (cf. the bromination of lepidine [4]), distillation of which caused decomposition and polymerisation (cf. the distillation of 4-iodoethylpyridine [5]); similar results were obtained in attempted dehydrobromination by methanolic potassium hydroxide.

* For a preliminary account, see *Proc. Chem. Soc.*, 1957, 352.

[1] Armit and Robinson, *J.*, 1922, **121**, 827; 1925, **127**, 1604.
[2] Prelog and Szpilfogel, *Helv. Chim. Acta*, 1945, **28**, 1684.
[3] Borsche, *Annalen*, 1910, **377**, 120; *Ber.*, 1908, **41**, 2203.
[4] Campbell, Ackermann, and Campbell, *J. Amer. Chem. Soc.*, 1949, **71**, 2905.
[5] Meisenheimer, *Annalen*, 1920, **420**, 190.

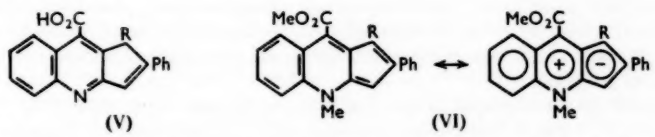
In a different approach we obtained a 64% yield of the 3-benzylidene-2 : 3-dihydro-β-quinindene when dihydro-β-quinindene was heated at 150° in a large excess of benzaldehyde. Ozonolysis of this product could be expected to give 2 : 3-dihydro-3-oxo-β-quinindene. However, ozonolysis in acetic acid [6] gave at most 15% yields of the ketone, and ozonolysis in carbon tetrachloride gave an ozonide which could not be decomposed. Anhydrous ethyl acetate was the best solvent for this ozonolysis provided that an excess of ozone (to which the ketone is sensitive) was avoided: a 64% yield of the ketone was then obtained if the ozonide was decomposed by hydrogen and platinum or palladium–charcoal.

Borsche *et al.* claim to have prepared two derivatives of this ketone but not the parent compound. They oxidised 2 : 3-dihydro-β-quinindene with selenium dioxide,[7] and distilled the reaction mixture; the distillate gave a small yield of a red 2 : 4-dinitrophenylhydrazone decomposing at 300°. Our ozonolysis product gave an orange dinitrophenylhydrazone decomposing between 275° and 295°. They [8] also prepared the phenylhydrazone by the series of reactions (A), obtaining it as a yellow powder, m. p. 170—173°, which on recrystallisation from benzene–hexane gave orange-red prisms, m. p. 113—114°. The phenylhydrazone from our ozonolysis product was bright yellow, crystallising from benzene as yellow needles, m. p. 176—177°. Our analyses for these derivatives were unsatisfactory and an alternative procedure was adopted. Oxidation of the benzylidene compound by osmium tetroxide gave a diol which was cleaved by lead tetra-acetate to a ketone identical with that obtained from the ozonolysis.

(A) 

Although substituted indenes are generally obtained from indan-1-one by a Grignard reaction followed by dehydration,[9] reaction of 2 : 3-dihydro-3-oxo-β-quinindene with phenylmagnesium bromide (or reduction by aluminium *iso*propoxide or borohydride) gave an insoluble blue material, not unlike that obtained on bromination. No explanation can be offered for the abnormal reaction.

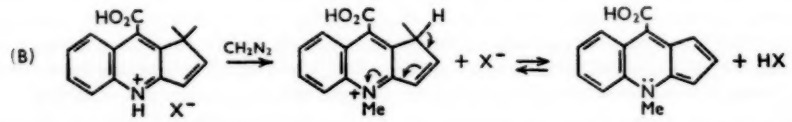
We next elaborated Borsche's synthesis of dihydro-β-quinindene. 3-Phenyl- and 3 : 4-diphenyl-*cyclo*pent-2-enone condensed smoothly with isatin in ethanolic potassium hydroxide to the β-quinindene acids (V; R = H and Ph). The similarity in properties and spectra of the derived methyl esters and ethyl 2-styrylcinchonate and their salts suggests that the double bond is in the 2 : 3- and not the alternative 1 : 2-position (cf. Boyd [10]).



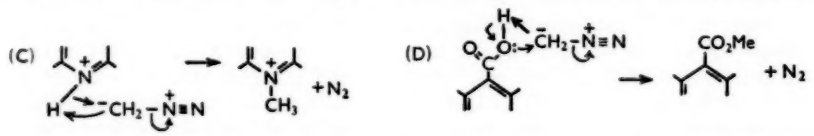
The acids (V) were insoluble in most organic solvents and crystallised only with difficulty (best from pyridine). In dilute solution they showed an intense blue fluorescence. The acid (V; R = H) slowly dissolved in ethereal diazomethane to a dark green solution. Chromatography on alumina separated two products, the colourless methyl ester of acid (V; R = H), and the intense blue anhydro-salt (VI; R = H) which was characterised as its 1 : 3 : 5-trinitrobenzene complex.

[6] Cf. Kaslow and Staynor, *J. Amer. Chem. Soc.*, 1945, **67**, 1716.
[7] Borsche and Hartmann, *Ber.*, 1940, **73**, 839.
[8] Borsche and Manteuffel, *Annalen*, 1938, **534**, 56.
[9] Cf., *e.g.*, Elsner and Parker, *J.*, 1957, 592.
[10] Boyd, *J.*, 1958, 1978.

The overall picture in the formation of the anhydronium salt is process (B). An acid-catalysed process is indicated since the ester of acid (V; R = H) does not react with diazomethane. The reactive species in this reaction, the diazonium ion, could



conceivably be produced by one or both of two processes, (C) and (D), giving both *N*- and *O*-methyl derivatives. Process (C) is shown to go through a zwitterion or intermolecular salt. Alternatively, intermolecular hydrogen-bonding between the carboxyl group and



the nitrogen produces the diazonium ion sufficiently close to both the nitrogen atom and the carboxyl group to allow competitive methylation.

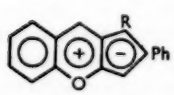
A similar reaction is observed with 8-hydroxyquinoline which yields the highly coloured *N*-methylquinolinium 8-oxide on treatment with diazomethane.

The anhydronium salt was also prepared by a three-stage process. The acid (V; R = H) with methanol and sulphuric acid yielded its methyl ester; with methyl iodide in benzene this gave the ester methiodide whence dilute sodium carbonate solution afforded the anhydronium salt (VI; R = H) whose trinitrobenzene complex was identical with that obtained by use of diazomethane. These reactions were also carried out with the homologous acid (V; R = Ph), with analogous results.

The acids (V; R = H or Ph) gave only small yields of decarboxylated material when distilled with soda-lime under reduced pressure. Less drastic methods failed completely. The methiodides of the resulting bases again gave intensely blue anhydronium salts on treatment with dilute carbonate solution.

All the anhydro-salts obtained from β-quinindene derivatives were violet or blue. In common with the azulenes, they formed crystalline, stable 1 : 3 : 5-trinitrobenzene complexes. Of the salts themselves, only one (VI; R = Ph) was obtained crystalline: it appeared to be stable. The other anhydronium salts were oils which decomposed in 24 hours; sunlight appeared to accelerate this. Azulenes and ylides suffer similarly and this has been attributed to the susceptibility of the carbanion to atmospheric oxidation.[11] With acids the blue anhydro-compounds form yellow salts possessing an intense blue fluorescence in solution.

Like Boyd,[10] we have prepared the analogous pyrylium compounds (VII; R = H and Ph). They were obtained in excellent yield by heating the salicylidene derivatives of 3-phenyl- and 3 : 4-diphenyl-*cyclo*pent-2-enone in acetic–hydrochloric acid. They are highly coloured (brownish-purple; blue-black) and much less basic than the nitrogen analogues: although they dissolve in strong mineral acids to give yellow, fluorescent pyrylium salts, they dissociate completely on dilution with water or attempted recrystallisation from an organic solvent.



(VII)

Spectra.—Azulenes show broad absorption in the visible and two bands in the ultraviolet region of the spectrum.[12] The visible part of the spectrum of azulene shows regular

[11] Saxena, Ph.D. Thesis, Edinburgh, 1955.
[12] See Gordon, *Chem. Rev.*, 1952, **50**, 185.

displacements with substitution. Direct comparison with our heterocyclic systems must be deferred until analogous azulenes are available, but some observations can already be made. (*a*) The β-quinindenes and the *cyclo*pentapyrans show the same general three-banded spectra as 5 : 6-benzazulene, the most closely related azulene known. (*b*) The relative displacements of the visible absorption band conform with expectations from azulene derivatives, except for identical visible absorption of compounds (VI; R = H and Ph), probably owing to molecular overcrowding which would prevent coplanarity of the 1-phenyl group with the rest of the molecule. (*c*) A direct comparison can be made between the analogous *cyclo*pentapyridines (VI; H in place of CO_2Me) and *cyclo*pentapyrans (VII). All show essentially the same three-banded spectra. The large difference

Ultraviolet and visible spectra (for ethanol solutions).

Compound	$\lambda_{max.}$ (mμ) and log ε (in parentheses)		
5 : 6-Benzazulene [13]	553(2·51)	352(3·55)	286(4·72)
			252(4·46)
(VI; R = H) *	574(3·06)	396(4·32)	297(4·51)
			232(4·45)
(VI; R = Ph) *	574(3·06)	396(4·41)	285(4·59)
4-Methyl-2-phenyl-β-quinindene *	532(3·01)	390(4·20), 370(4·30)	279(4·47)
4-Methyl-1 : 2-diphenyl-β-quinindene *	554(3·21)	372(4·33)	285(4·58)
(VII; R = H)	470(2·71)	387(4·37), 368(4·56)	256(4·52)
(VII; R = Ph)	512(2·92)	366(4·47)	265(4·54)

* 1 : 3 : 5-Trinitrobenzene complexes.

in $\lambda_{max.}$ (see Table) in the visible part of the spectrum must be attributed to the difference in the heteroatoms. Oxygen, being more electronegative than nitrogen, will show a greater tendency to develop an electron pair, so that there will be a greater contribution from the purely covalent structure (cf. Ia) and a smaller contribution from the dipolar structure (cf. Ib) and hence a decrease in depth of colour and basicity in the oxygen series.

Experimental

M. p. (uncorr.) taken on a hot stage.

2 : 3-*Dihydro*-β-*quinindene*.—2 : 3-Dihydro-β-quinindene-9-carboxylic acid was prepared in 90% yield.[3] Refluxing in methanol–sulphuric acid gave the *methyl ester* crystallising from aqueous methanol as prisms, m. p. 74—75° (Found: C, 73·7; H, 5·9; N, 5·9. $C_{14}H_{13}O_2N$ requires C, 73·9; H, 5·7; N, 6·2%). The acid (52 g.) was heated in a vacuum until the evolution of carbon dioxide had ceased and the residue was distilled. The distillate was dissolved in ether, washed with sodium carbonate solution and water, and dried (Na_2SO_4). Removal of the solvent gave a viscous oil which was distilled under reduced pressure to give 2 : 3-dihydro-β-quinindene (30 g., 71%), m. p. 59—60° (lit., m. p. 59—60°).

3-*Benzylidene*-2 : 3-*dihydro*-β-*quinindene*.—2 : 3-Dihydro-β-quinindene (30 g.) and freshly distilled benzaldehyde (50 g.) were heated at 150° for 4 hr., water distilling as it was formed. Excess of benzaldehyde was removed by distillation, and the residue triturated with ethanol (30 ml.). The solid was collected and recrystallised from ethanol in which it had a strong blue fluorescence. *3-Benzylidene-2 : 3-dihydro-β-quinindene* (29 g., 64%) crystallised as colourless needles, m. p. 119—120° (Found: C, 88·7; H, 5·9; N, 5·4. $C_{19}H_{15}N$ requires C, 88·7; H, 5·8; N, 5·4%). The *methosulphate* separated from ethanol as yellow plates, m. p. 170—220° (Found: C, 65·6; H, 5·4; N, 3·6; S, 8·5. $C_{21}H_{21}O_4NS$ requires C, 65·8; H, 5·5; N, 3·7; S, 8·4%).

2 : 3-*Dihydro*-3-*oxo*-β-*quinindene*.—(*a*) Ozonised oxygen (~5%) was passed through a solution of the benzylidene compound (2 g.) in anhydrous ethyl acetate (80 ml.) at 0° until issuing in excess (starch–iodide). After nitrogen had been passed through the solution for 15 min., Adams catalyst (25 mg.) was added and a slow stream of hydrogen bubbled through the solution for 1 hr. Ethanol (25 ml.) was added and the solution heated to boiling and filtered. Removal of the solvent gave a yellow residue. Crystallisation from ethanol gave

[13] Kloster-Jenson, Kovats, Eschenmoser, and Heilbronner, *Helv. Chim. Acta*, 1956, **39**, 1058.

2 : 3-*dihydro*-3-*oxo*-β-*quinindene* (0·9 g., 64%) as colourless plates, m. p. 183—184° (decomp.) (Found: C, 77·6, 77·8, 77·4; H, 4·8, 5·2, 4·7; N, 8·0, 7·6, 6·7. $C_{12}H_9ON$ requires C, 78·7; H, 4·9; N, 7·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from acetic acid as yellow-orange needles, decomp. 275—295° (Found: C, 57·5, 57·7, 57·5; H, 3·9, 4·8, 3·8; N, 17·5, 18·2, 18·8. $C_{18}H_{13}O_4N_5$ requires C, 59·5; H, 3·6; N, 19·3%), the *phenylhydrazone* from benzene as yellow needles, m. p. 176—177° (Found: C, 78·3, 78·0; H, 6·0, 5·7; N, 11·5. $C_{18}H_{15}N_3$ requires C, 79·1; H, 5·5; N, 15·4%), and the *oxime* from ethanol as colourless prisms, m. p. 230—232° (decomp.) (Found: C, 72·2; H, 4·6; N, 11·8. $C_{12}H_{10}ON_2$ requires C, 72·8; H, 5·0; N, 14·1%).

(*b*) Osmium tetroxide (1 g.) was added to a solution of the benzylidene compound (2 g.) in anhydrous ether (200 ml.) containing anhydrous pyridine (5 ml.), and the mixture kept at room temperature for 3 hr. The chocolate-brown precipitate (2·37 g.) was collected, washed with ether, added to potassium hydroxide (1 g.) and mannitol (10 g.) in water (100 ml.) and chloroform (30 ml.), and shaken for 24 hr. The chloroform layer was separated, dried, and evaporated, to give a solid residue. A light petroleum (b. p. 40—60°) extract precipitated cis-2 : 3-*dihydro*-3-*hydroxy*-3-(α-*hydroxybenzyl*)-β-*quinindene* which was recrystallised from benzene–1-methylheptane as white plates, m. p. 139—140° (Found: C, 78·1; H, 6·0; N, 4·7. $C_{19}H_{17}O_2N$ requires C, 78·3; H, 5·8; N, 4·8%).

This glycol (0·22 g.) and lead tetra-acetate (0·33 g.) in benzene (50 ml.) were shaken for 3 hr. After removal of the benzene, the residue crystallised from ethanol as colourless plates, m. p. 183—184° (decomp.) alone or mixed with the ozonolysis product.

2-*Phenyl*-β-*quinindene*-9-*carboxylic Acid* (V; R = H).—Solutions of isatin (5·3 g.) in 30% potassium hydroxide solution (30 ml.) and 3-phenyl*cyclo*pent-2-enone [14] (5·0 g.) in ethanol (65 ml.) were heated under reflux for 6 hr. The ethanol was then distilled off, water (200 ml.) added, and the solution filtered. Addition of excess of 50% acetic acid precipitated a green-yellow solid which was collected and washed with water (500 ml.) and ethanol (50 ml.). This 2-*phenyl*-β-*quinindene*-9-*carboxylic acid* (7 g.) is pure enough for most purposes but recrystallises from pyridine as yellow needles, m. p. 260—290° (decomp.) (Found: C, 75·0; H, 4·9; N, 4·1. $C_{19}H_{13}O_2N,H_2O$ requires C, 74·9; H, 4·9; N, 4·6%).

Methyl 4-*Methyl*-2-*phenyl*-β-*quinindene*-9-*carboxylate* (VI; R = H).—(*a*) 2-Phenyl-β-quinindene-9-carboxylic acid was added to an excess of diazomethane in dry ether. The acid disappeared within 4 hr. with slow evolution of nitrogen. The intense red-purple solution was filtered and the solvent removed. A light petroleum (b. p. 40—60°) extract deposited colourless crystals from a vivid blue solution. These crystals recrystallised from methanol as colourless prisms, m. p. 135—136°, not depressed on admixture with the methyl 2-phenyl-β-quinindene-9-carboxylate obtained as in (*b*) below. The supernatant liquid was evaporated and the residue chromatographed in benzene on alumina, giving a green and a colourless band, the latter having a strong blue fluorescence in ultraviolet light. Elution with benzene gave the green band as a vivid blue solution and the colourless band as a highly fluorescent solution. The colourless band gave a further quantity of the methyl ester. The oil obtained from the blue solution formed a *complex* with 1 : 3 : 5-trinitrobenzene from methanol; this recrystallised from methanol as brown-black needles, m. p. 154—155° (Found: C, 61·2; H, 3·8; N, 10·2. $C_{27}H_{20}O_8N_4$ requires C, 61·4; H, 3·8; N, 10·6%).

(*b*) 2-Phenyl-β-quinindene-9-carboxylic acid with methanol and sulphuric acid gave the *methyl ester*, m. p. 135—136°, identical with that obtained as above (Found: C, 79·7; H, 4·9; N, 4·4. $C_{20}H_{15}O_2N$ requires C, 79·7; H, 5·0; N, 4·7%). The ester was boiled under reflux in benzene containing an excess of methyl iodide for 3 hr. The *methiodide* was collected and recrystallised from aqueous methanol as yellow prisms which did not melt up to 320° (Found: C, 57·1; H, 4·4; N, 2·6; I, 22·2. $C_{21}H_{18}O_2NI$ requires C, 56·9; H, 4·1; N, 3·2; I, 28·6%). The methiodide was suspended in 10% sodium carbonate solution and shaken with chloroform. The chloroform layer was separated, dried, and evaporated, to give a blue oil which readily formed a trinitrobenzene complex in methanol: the brown-black crystals had m. p. 154—155° undepressed on admixture with the complex obtained as in (*a*).

Methyl 4-*Methyl*-1 : 2-*diphenyl*-β-*quinindene*-9-*carboxylate* (VI; R = Ph).—Isatin (18 g.) and 3 : 4-diphenyl*cyclo*pent-2-enone [15] (20 g.) gave 1 : 2-*diphenyl*-β-*quinindene*-9-*carboxylic acid* (20 g., 65%), crystallising from pyridine as bright yellow needles, m. p. 282—284° (Found:

[14] Mousseron and Rouzier, *Bull. Soc. chim. France*, 1953, 190.
[15] Japp and Knox, *J.*, 1905, **87**, 673.

C, 75·3; H, 5·7; N, 3·4. $C_{25}H_{17}O_2N,2H_2O$ requires C, 75·2; H, 5·3; N, 3·5%), and giving with diazomethane the *methyl ester*, m. p. 170—172° (Found: C, 83·0; H, 4·7; N, 3·3. $C_{26}H_{19}O_2N$ requires C, 82·8; H, 5·1; N, 3·7%), and the blue *methyl* 4-*methyl*-1 : 2-*diphenyl*-β-*quinindene*-9-*carboxylate*, black prisms (from methanol), m. p. 178—179° (Found: C, 82·9; H, 5·1; N, 3·7. $C_{27}H_{21}O_2N$ requires C, 82·8; H, 5·4; N, 3·6%). Methyl 1 : 2-diphenyl-β-quinindene-9-carboxylate gave an orange *methiodide*, m. p. 215° (decomp.) (Found: C, 62·7; H, 4·6; N, 2·4; I, 19·4. $C_{27}H_{22}O_2NI$ requires C, 62·5; H, 4·2; N, 2·7; I, 24·5%). With sodium carbonate solution the methiodide gave the blue anhydro-salt identical with that obtained by use of diazomethane.

4-*Methyl*-1 : 2-*diphenyl*-β-*quinindene*.—A mixture of soda-lime (2 g.) and 1 : 2-diphenyl-β-quinindene-9-carboxylic acid (0·5 g.) was covered with soda-lime (1 g.) in a hard-glass tube attached to a U-tube immersed in ice-water and evacuated (water-pump). The tube was heated gradually. A buff-coloured solid which collected in the U-tube was extracted in ether, washed with sodium carbonate solution, and dried. The *product* remaining on removal of the solvent crystallised from ethanol as colourless needles (0·1 g.), m. p. 187—188° (Found: C, 90·0; H, 5·8; N, 4·4. $C_{24}H_{17}N$ requires C, 90·3; H, 5·3; N, 4·4%). The methiodide crystallised from chloroform–ether as yellow prisms, m. p. 193—194° (decomp.), and with sodium carbonate solution gave the blue 4-methyl-1 : 2-diphenyl-β-quinindene characterised as its *trinitrobenzene complex* which crystallised from methanol as black prisms, m. p. 181—182° (Found: C, 68·2; H, 4·0; N, 9·9. $C_{31}H_{22}O_6N_4$ requires C, 68·1; H, 4·0; N, 10·3%).

4-*Methyl*-2-*phenyl*-β-*quinindene*.—Decarboxylation of 2-diphenyl-β-quinindene-9-carboxylic acid, as above, gave a product which could not be purified and was converted into its methiodide which crystallised from ethanol–ether as yellow-green prismatic needles, m. p. 203—205°, and with sodium carbonate gave the blue 4-methyl-2-phenyl-β-quinindene characterised as its *trinitrobenzene complex*, black prisms (from methanol), m. p. 144—145° (Found: C, 63·7; H, 3·6; N, 12·6. $C_{25}H_{18}O_6N_4$ requires C, 63·8; H, 3·8; N, 11·9%).

2-*Phenylbenzo*[b]cyclo*penta*[e]*pyran*.—The procedure was identical with that described by Boyd.[10] Our product had m. p. 208—209°. Boyd gives m. p. 207—207·5°.

1 : 2-*Diphenylbenzo*[b]cyclo*penta*[e]*pyran*.—3 : 4-Diphenyl*cyclo*pent-2-enone (3 g.) and salicylaldehyde (1·6 g.) in ethanol in the presence of a small quantity of piperidine acetate were boiled under reflux for 3 hr. Removal of the solvent left a dark red oil which was dissolved in acetic acid (45 ml.) and concentrated hydrochloric acid (5 ml.). After 2 hours' heating at 90°, the solution was poured into water (250 ml.), and the purple precipitate collected, washed with water, and dried (P_2O_5). The solid (3 g., 73%) crystallised from ethanol as blue-black prisms (dark red by transmitted light), m. p. 155—156° (Found: C, 88·8; H, 5·0. $C_{24}H_{16}O$ requires C, 90·0; H, 5·0%).

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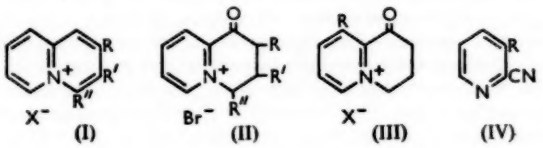
334. *Quinolizines. Part III.*[1] *The Synthesis of 1-Alkyl- and 1-Aryl-quinolizinium Salts.*

By E. E. Glover and Gurnos Jones.

Some γ-2′-pyridylbutyraldehyde diethyl acetals have been prepared. With boiling hydrobromic acid they give, in most cases, 1,2-dihydroquinolizinium derivatives, and thence the quinolizinium salts. 1-Methylquinolizinium picrate has also been obtained by a modification of a previous quinolizinium synthesis.[2]

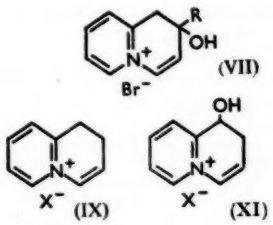
We have reported [1] the preparation of quinolizinium salts (I) bearing alkyl or aryl groups in the 2-, 3-, or 4-position, by the action of boiling acetic anhydride on ketones of type (II). Although this method represents a possible route to 1-substituted quinolizinium salts (XVII), the precursor (III) would have to be prepared from a 3-substituted 2-cyanopyridine (IV) and such compounds are difficult to prepare in quantity. In the present paper we report attempts to find a more convenient route to 1-alkyl- and 1-aryl-quinolizinium salts (XVII).



(I) (II) (III) (IV)

By preparing hydroxy-acetals of type (V) we hoped to obtain, after cyclisation with acid and dehydration of the cyclised alcohol, 1-substituted quinolizinium salts (cf. V ⟶ XVI ⟶ XVII). When our preliminary experiments were complete Nesmeyanov and Rybinskaia reported [3] the preparation of hydroxy-acetals of type (VI; R = Me, Pr^n, or Ph), which were cyclised in boiling hydrobromic acid to the hydroxy-compound (VII) and these were dehydrated to give 2-substituted quinolizinium salts (I; R = Me, Pr^n, or Ph, R′ = R″ = H).

(V) 2-C_5H_4N·CR(OH)·$[CH_2]_3$·CH(OEt)$_2$
(VI) 2-C_5H_4N·CH_2·CR(OH)·CH_2·CH(OEt)$_2$
(VIII) 2-C_5H_4N·$[CH_2]_3$·CH(OEt)$_2$
(X) R·$[CH_2]_3$·CH(OEt)$_2$



(VII) (IX) (XI)

First we treated γ-2′-pyridylbutyraldehyde diethyl acetal [4] (VIII) with boiling concentrated hydrobromic acid for 3 hr., but could not isolate any pure material. 18 hours' reaction gave 1,2-dihydroquinolizinium picrate (IX; X = picrate) but only in poor yield [the 1,2-dihydro-structure is assumed from the mode of formation and from the difference in ultraviolet absorption of the product from that of 3,4-dihydro-1-methylquinolizinium picrate (XX; X = picrate)].

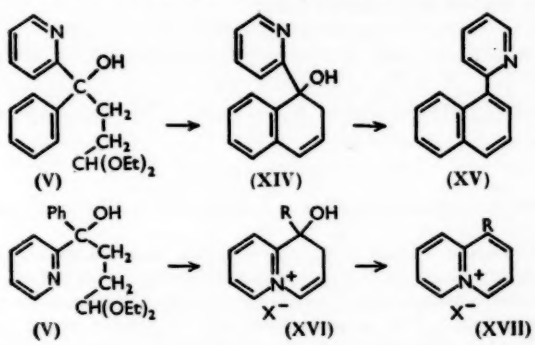
Next we tried to prepare the parent quinolizinium cation by cyclisation of γ-hydroxy-γ-2′-pyridylbutyraldehyde diethyl acetal (V; R = H) with subsequent dehydration of the hydroxy-compound (XI). We obtained the acetal (V; R = H) by a novel reaction.

[1] Part II, Glover and Jones, *J.*, 1958, 3021.
[2] Boekelheide and Gall, *J. Amer. Chem. Soc.*, 1954, **76**, 1832.
[3] Nesmeyanov and Rybinskaia, *Doklady Akad. Nauk. S.S.S.R.*, 1957, **116**, 93.
[4] Jones and Law, *J.*, 1958, 3631.

β-Bromopropionaldehyde diethyl acetal (X; R = Br) reacted smoothly with lithium in dry ether. Adding to pyridine-2-aldehyde a solution containing an excess of this lithium reagent (X; R = Li) afforded a complex from which a 61% yield of the hydroxy-acetal (V; R = H) was obtained. However, attempts to cyclise this to the 1,2-dihydro-1-hydroxyquinolizinium salt (XI) gave only tars. In the hope that the unsaturated acetal (XII) might be more readily cyclised, the hydroxy-acetal (V; R = H) was heated with acetic anhydride; after hydrolysis of the acetic anhydride, a picrate was obtained whose analyses appear to indicate that it is the picrate of 4-acetoxy-4-2′-pyridylbutyraldehyde (XIII; R = Ac, R′ = H).

$2\text{-}C_5H_4N\cdot CH{:}CH\cdot CH_2\cdot CH(OEt)_2$ (XII) $2\text{-}C_5H_4N\cdot CR'(OR)\cdot[CH_2]_2\cdot CHO$ (XIII)

We next prepared the hydroxy-acetal (V; R = Ph) by interaction of the lithium reagent (X; R = Li) with 2-benzoylpyridine. When this acetal was boiled with hydrobromic acid for 5 hr. it afforded much tar and a material from which two isomeric picrates were prepared. The higher-melting was identified by analysis and mixed melting point as α-2-pyridylnaphthalene picrate,[5] formed by the reactions (V) ⟶ (XIV) ⟶ (XV). The lower-melting picrate was smoothly converted into a perchlorate by anionic exchange; its ultraviolet absorption spectrum was similar to that of 2-phenylquinolizinium perchlorate,[1] therefore it is considered to be the desired 1-phenylquinolizinium picrate (XVII; R = Ph, X = picrate). In impure samples were found traces of a third picrate; this was suspected of being an intermediate, so the acetal (V; R = Ph) was then boiled with hydrobromic acid for 1·5 hr. only and then gave only the third picrate; analyses were in closest agreement with a formulation $C_{15}H_{15}O_2N$ + picrate and of the possible intermediates (XIII; R = H, R′ = Ph), (XIV), and (XVI), the first appears the most likely.



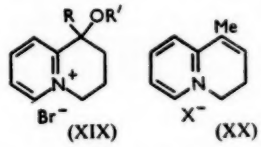
Attempts to prepare the hydroxyvaleraldehyde diethyl acetal (V; R = Me) by a similar reaction were unsuccessful. When a solution of the lithium reagent (X; R = Li) was added to a solution of 2-acetylpyridine, a complex was formed, but decomposition of this complex gave only 2-acetylpyridine. Since 2-acetyl-5-methylpyridine has been reported [6] to react normally with methylmagnesium iodide, we assume that the failure of the above reaction is due to some complex formation between the lithium ion and the 2-acetylpyridine. In confirmation of the above report we treated 2-acetylpyridine with 3-ethoxypropylmagnesium bromide or chloride: each gave a good yield of the pyridyl-alcohol (XVIII; R = Me) which was cyclised by treatment with boiling hydrobromic acid and subsequent heating of the intermediate bromo-amine in chloroform, giving the tetrahydrohydroxyquinolizinium bromide (XIX; R = Me, R′ = H). This was dehydrated to a 3,4-dihydro-1-methylquinolizinium salt (XX), and the picrate (XX;

[5] Bradsher and Beavers, *J. Amer. Chem. Soc.*, 1956, **78**, 2459.
[6] Oparin *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 2011; *Chem. Abs.*, 1930, **24**, 4785.

X = picrate) was dehydrogenated by palladium–charcoal in boiling butanol to 1-methylquinolizinium picrate (XVII; R = Me, X = picrate). The perchlorate (XVII; R = Me, X = ClO_4) showed the characteristic quinolizinium absorption in the ultraviolet region. In one experiment the dehydration procedure was modified; on cooling the acetic anhydride solution crystals separated. These were shown by analysis to be the acetate (XIX; R = Me, R′ = Ac). The synthesis reported above is a modification of that used by Boekelheide and Gall in their synthesis of quinolizinium salts.[2]

Since 3-ethoxypropylmagnesium bromide reacted successfully with 2-acetylpyridine, attempts were made to prepare a Grignard reagent of type (X; R = MgX). Neither 3-bromo- nor 3-chloro-propionaldehyde diethylacetal could be made to react with magnesium in ether, but in tetrahydrofuran the chloroacetal gave the Grignard reagent smoothly. This, with 2-acetylpyridine, gave a complex from which the hydroxy-acetal (V; R = Me)

2-C_5H_4N·CR(OH)·[CH_2]$_3$·OEt
(XVIII)



(XIX) (XX)

was obtained in 48% yield. This acetal with boiling hydrobromic acid gave a gum from which the picrate of the cyclic alcohol (XVI; R = Me, X = picrate) was obtained. The unpurified gum [assumed to be the bromide (XVI; R = Me, X = Br)] was boiled in acetic anhydride containing a trace of sulphuric acid, affording 1-methylquinolizinium as picrate, identical with that obtained by the method reported above. The overall yield from the hydroxy-acetal (V; R = Me) was 54%, so that this sequence of reactions offers a satisfactory route to the 1-alkylquinolizinium salts.

In an attempt to prepare 1-phenylquinolizinium picrate by an unambiguous route, 2-benzoylpyridine was treated with 3-ethoxypropylmagnesium bromide, giving the phenylpyridyl-alcohol (XVIII; R = Ph). However, attempts to cyclise this compound to the hydroxyquinolizinium compound (XIX; R = Ph, R′ = H) were unsuccessful.

Experimental

M. p.s were determined on a Kofler block. Reactions with lithium reagents were performed in dry nitrogen.

1,2-Dihydroquinolizinium Picrate (IX; X = *Picrate*).—A solution of γ-2′-pyridylbutyraldehyde diethyl acetal[4] (2 g.) in 48% aqueous hydrobromic acid (25 ml.) was boiled under reflux for 18 hr. After evaporation to dryness under reduced pressure the residue was treated with water and chloroform. The aqueous layer was evaporated under reduced pressure to small volume and treated with saturated aqueous sodium picrate. The precipitated picrate and the supernatant liquor were heated on a boiling-water bath, and the clear supernatant liquor was decanted. The residual gummy picrate was treated with acetone and set aside overnight, after which filtration gave a solid yellow *picrate* (140 mg.), recrystallising from water as yellow prisms, m. p. 183° (Found: C, 50·0; H, 3·5. $C_{15}H_{12}O_7N_4$ requires C, 50·1; H, 3·4%), $\lambda_{max.}$ 3150, 3290, 3570 Å ($\log_{10}\varepsilon$ 3·94, 4·2, 4·15) in ethanol.

γ-Hydroxy-γ-2′-pyridylbutyraldehyde Diethyl Acetal (V; R = H).—The lithium reagent from β-bromopropionaldehyde diethyl acetal[7] (40 g.; freshly distilled) and lithium (2·7 g.) in anhydrous ether (200 ml.) was added slowly to a cold, stirred solution of pyridine-2-aldehyde (10 g.) in anhydrous ether (100 ml.). The mixture was subsequently stirred for 1 hr. and left overnight. The complex obtained was decomposed by water, and the ethereal layer was dried (Na_2SO_4) and distilled, giving the *acetal*, b. p. 173—176°/12 mm., 113°/0·1 mm. (13·7 g., 61%) (Found: C, 64·8; H, 8·9. $C_{13}H_{21}O_3N$ requires C, 65·2; H, 8·8%). The *acetal picrate* crystallised from absolute ethanol as needles, m. p. 116—117° (Found: C, 48·6; H, 4·7. $C_{19}H_{24}O_{10}N_4$ requires C, 48·7; H, 5·2%).

[7] Nef, *Annalen*, 1904, **335**, 363.

γ-Acetoxy-γ-2′-pyridylbutyraldehyde Picrate (XIII; R = Ac, R′ = H).—γ-Hydroxy-γ-2′-pyridylbutyraldehyde diethyl acetal (2 g.) was boiled in acetic anhydride (15 ml.) for 10 min. After addition of water the solvent was removed under reduced pressure. The residue was dissolved in the minimum quantity of 2N-hydrochloric acid, diluted, and treated with an excess of saturated aqueous sodium picrate. The *picrate* (1·7 g., 58%) crystallised from water as prisms, m. p. 130—131° (Found: C, 46·8; H, 3·6. $C_{17}H_{16}O_{10}N_4$ requires C, 46·8; H, 3·7%).

2-Benzoylpyridine.—A cooled, stirred solution of 2-cyanopyridine (20 g.) in dry ether (150 ml.) under nitrogen was treated dropwise with the Grignard reagent from bromobenzene (40 g.) in dry ether (400 ml.). The mixture was stirred for 1 hr. and left overnight. The Grignard complex was hydrolysed by ice-cold 5N-hydrochloric acid, the whole basified, and the base extracted with ether and dried (Na_2SO_4). Distillation gave 2-benzoylpyridine, b. p. 107°/0·1 mm. (30 g., 85%).

2-Acetylpyridine.—This, b. p. 84—86°/16 mm., was similarly prepared in 77% yield from 2-cyanopyridine and methylmagnesium iodide.

γ-Hydroxy-γ-phenyl-γ-2′-pyridylbutyraldehyde Diethyl Acetal (V; R = Ph).—A cooled, stirred solution of 2-benzoylpyridine (15 g.) in anhydrous ether (100 ml.) was treated dropwise with the lithium reagent from β-bromopropionaldehyde diethyl acetal [7] (40 g.) and lithium (2·7 g.) in anhydrous ether (200 ml.). Worked up as described for compound (V; R = H) the *hydroxy-acetal* was obtained as an oil, b. p. 160°/0·1 mm. (17 g., 66%) (Found: C, 72·2; H, 8·1. $C_{19}H_{25}O_3N$ requires C, 72·3; H, 8·0%).

On one occasion, under the conditions described above but with the lithium reagent added rapidly to the benzoylpyridine, the material, isolated in 80% yield, had b. p. 130—134°/0·1 mm. and solidified. Recrystallisation from light petroleum (b. p. 60—80°) gave prisms of phenyl-2-pyridylmethanol, m. p. 74° (lit.,[8] m. p. 76—78°). The picrate crystallised from absolute ethanol as prisms, m. p. 169° (lit.,[8] m. p. 169°).

1-Phenylquinolizinium Picrate (XVII; R = Ph, X = *Picrate*) *and α-2-Pyridylnaphthalene* (XV) *Picrate.*—A solution of the acetal (V; R = Ph) (3 g.) in 48% aqueous hydrobromic acid (25 ml.) was boiled under reflux for 5 hr. Evaporation to dryness under reduced pressure gave a residue which was treated with water and filtered from a black solid. The filtrate was washed with chloroform and evaporated under reduced pressure. Two methods were used to work up the residue. (*a*) The residue was dissolved in a small volume of water and treated with an excess of a saturated aqueous sodium picrate. The precipitate and the supernatant picrate solution were heated for some time at 100° and then filtered hot. From the filtrate, on cooling, crystallised *1-phenylquinolizinium picrate* (0·21 g.), needles (from absolute ethanol), m. p. 128°, rising to 160° on drying at 118°/0·1 mm. (Found: C, 58·1; H, 3·2. $C_{21}H_{14}O_7N_4$ requires C, 58·05; H, 3·25%), $\lambda_{max.}$ 2310 Å ($\log_{10}$ ε 4·4) in water. The *perchlorate*, obtained by anionic exchange on an Amberlite I.R.A.-400 column, crystallised from absolute ethanol–ethyl acetate as needles, m. p. 150—151° (Found: C, 58·5; H, 3·9. $C_{15}H_{12}O_4NCl$ requires C, 58·9; H, 4·0%), $\lambda_{max.}$ 2930, 3220, 3300 Å ($\log_{10}$ ε 3·87, 4·02, 4·13) in water.

The material undissolved by the hot sodium picrate solution was crystallised first from water and then from absolute ethanol, forming yellow needles, m. p. 194—195° (recorded [5] m. p. of α-2-pyridylnaphthalene picrate 198°) (Found: C, 58·3; H, 3·2. Calc. for $C_{21}H_{14}O_7N_4$: C, 58·05; H, 3·25%). A mixed m. p. with a synthetic sample of α-2-pyridylnaphthalene picrate showed no depression.

(*b*) If the residue was treated with alcoholic picric acid and the precipitate collected and digested with hot water as above the main product isolated was the α-2-pyridylnaphthalene picrate (0·32 g.) with a much smaller quantity of 1-phenylquinolizinium picrate (0·09 g.).

In one experiment the hydroxy-acetal (VII; R = Ph) was boiled with hydrobromic acid for a shorter time (1·5 hr.). Working up by method (*a*) gave a *picrate*, m. p. 168°, as prisms from absolute ethanol (Found: C, 52·8, 52·9; H, 3·7, 3·5. $C_{21}H_{18}O_9N_4$ requires C, 53·6; H, 3·9%).

Treatment of 2-Acetylpyridine with 3,3-Diethoxypropyl-lithium.—To a cooled, stirred solution of 2-acetylpyridine (10 g.) in anhydrous ether (100 ml.) was added dropwise the lithium reagent from β-bromopropionaldehyde diethyl acetal (40 g.). A white complex was formed and was decomposed next morning by water. After drying (Na_2SO_4) the ethereal layer was distilled: 2-acetylpyridine (6 g.) was recovered. None of the expected alcohol was obtained.

5-Ethoxy-2-2′-pyridylpentan-2-ol (XVIII; R = Me).—2-Acetylpyridine (10 g.) in anhydrous ether (50 ml.) was added under nitrogen to the stirred Grignard reagent from 3-ethoxypropyl

[8] Gilman and Spatz, *J. Org. Chem.*, 1951, **16**, 1485

bromide [10] (20 g.) in anhydrous ether (250 ml.). Stirring was continued for 1 hr. after the addition, and the mixture then left overnight. The complex was decomposed by cold 5N-hydrochloric acid, and the aqueous layer was basified and extracted with ether. The ethereal extract was dried (Na_2SO_4) and distilled, giving the *pyridylpentanol* (10·5 g., 59%), b. p. 160—162°/17 mm. (Found: C, 69·05; H, 9·3. $C_{12}H_{19}O_2N$ requires C, 68·9; H, 9·15%). The yield was similar when the Grignard reagent from 3-ethoxypropyl chloride was used, and since this can be obtained from 3-ethoxypropanol in better yield (73%) than the bromide (60%) it is the preferred reagent.

1,2,3,4-*Tetrahydro*-1-*hydroxy*-1-*methylquinolizinium Bromide* (XIX; R = Me, R′ = H).—A solution of the pentanol (XVIII; R = Me) (3 g.) in 48% aqueous hydrobromic acid (20 ml.) was boiled under reflux for 0·5 hr. The solution was evaporated to dryness under reduced pressure, the residue dissolved in water and basified by aqueous sodium carbonate, and the liberated bromo-amine was extracted by benzene. The dried (Na_2SO_4) benzene solution was boiled under reflux until a solid separated. Filtration gave the *tetrahydroquinolizinium bromide* (1·05 g., 30%) as a colourless solid, crystallising from absolute ethanol–ethyl acetate as prisms, m. p. 156° (Found: C, 49·2; H, 5·8. $C_{10}H_{14}ONBr$ requires C, 49·2; H, 5·9%), $\lambda_{max.}$ 2660 Å ($\log_{10}$ ε 3·83) in water. The *picrate* crystallised from absolute ethanol as prisms, m. p. 128° (Found: C, 49·15; H, 4·1. $C_{16}H_{16}O_8N_4$ requires C, 49·0; H, 4·1%).

1-*Acetoxy*-1,2,3,4-*tetrahydro*-1-*methylquinolizinium Bromide* (XIX; R = Me, R′ = Ac).—A solution of 1,2,3,4-tetrahydro-1-hydroxy-1-methylquinolizinium bromide (1 g.) in acetic anhydride (6 ml.) containing a drop of sulphuric acid was boiled under reflux for 10 min. The solution was cooled and the solid was filtered off. Treatment of the filtrate with ethyl acetate precipitated more solid which was filtered off and added to the initial precipitate. The combined precipitates crystallised from ethyl acetate–ethanol as prisms, m. p. 212° (0·8 g., 68%) (Found: C, 50·4; H, 5·8. $C_{12}H_{16}O_2NBr$ requires C, 50·35; H, 5·6%), $\lambda_{max.}$ 2680 Å ($\log_{10}$ ε 3·91) in water. The *picrate*, prepared by treating the solid bromide with saturated aqueous sodium picrate, crystallised from absolute alcohol as prisms, m. p. 142° (Found: C, 49·6; H, 4·2. $C_{18}H_{18}O_9N_4$ requires C, 49·8; H, 4·2%).

3,4-*Dihydro*-1-*methylquinolizinium Picrate* (XX).—A solution of the hydroxyquinolizinium bromide (XIX; R = Me, R′ = H) (1 g.) in acetic anhydride (20 ml.) containing a drop of sulphuric acid was boiled under reflux for 0·5 hr., then cooled, water was added, and the volume reduced to 3 ml. under reduced pressure. Dilution followed by addition of saturated aqueous sodium picrate gave the dihydroquinolizinium picrate, crystallising from absolute ethanol as prisms, m. p. 114—115° (0·8 g., 53%) (Found: C, 50·8; H, 3·8. $C_{16}H_{14}O_7N_4$ requires C, 51·35; H, 3·8%), $\lambda_{max.}$ 3325 Å ($\log_{10}$ ε 4·18) in 95% ethanol.

Dehydrogenation of 3,4-*Dihydro*-1-*methylquinolizinium Picrate*.—A solution of the dihydroquinolizinium picrate (0·4 g.) in butanol was boiled under reflux for 3 hr. with 5% palladium–charcoal [11] (0·4 g.). The solution was then filtered hot and cooled, 1-methylquinolizinium picrate crystallising (0·11 g., 27%). Recrystallised from absolute ethanol it had m. p. 149°, and was identical with that prepared as described below.

γ-*Hydroxy*-γ-2′-*pyridylvaleraldehyde Diethyl Acetal* (V; R = Me).—A solution of the Grignard reagent from 3-chloropropionaldehyde diethyl acetal [9] (27 g.) and magnesium (3·9 g.) in tetrahydrofuran (120 ml.) was prepared under nitrogen and stirred for 1 hr. after addition of the chloro-compound. 2-Acetylpyridine (10 g.) in tetrahydrofuran (50 ml.) was added slowly, the solution being boiled for a further 15 min. and then stirred until it had reached room temperature. The mixture was hydrolysed with an aqueous mixture of ammonia and ammonium chloride, and the aqueous layer washed with ether. The combined organic layer and ether extracts were dried (Na_2SO_4) and distilled, giving the *hydroxyvaleraldehyde diethyl acetal* (10 g., 48%), b. p. 116°/0·4 mm. (Found: C, 66·45; H, 8·9; N, 5·15. $C_{14}H_{23}O_3N$ requires C, 66·4; H, 9·15; N, 5·5%).

1-*Methylquinolizinium Picrate* (XVII; R = Me, X = *Picrate*).—A solution of the acetal (V; R = Me) (3 g.) in 48% aqueous hydrobromic acid (25 ml.) was boiled under reflux for 3 hr. Working up as described for the phenylquinolizinium compound gave an aqueous solution which on evaporation yielded a brown gum; this was treated with alcohol and evaporated to dryness, but failed to crystallise. A sample, dissolved in water and treated with saturated aqueous

[9] Witzemann, Evans, Hass, and Schroeder, *Org. Synth.*, Coll. Vol. II, p. 137.
[10] Hurd and Fowler, *J. Amer. Chem. Soc.*, 1939, **61**, 249.
[11] Schwyzer, *Helv. Chim. Acta*, 1952, **35**, 867.

sodium picrate solution, gave **1,2-*dihydro*-1-*hydroxy*-1-*methylquinolizinium picrate*** (XVI; R = Me, X = picrate), crystallising from absolute alcohol as prisms, m. p. 152—153° (Found: C, 49·2; H, 3·7. $C_{16}H_{14}O_8N_4$ requires C, 49·2; H, 3·6%).

The major portion of the gum was boiled in acetic anhydride (15 ml.) containing a trace of concentrated sulphuric acid for 0·5 hr. The cooled solution was treated with ether, and the black oil which was precipitated was separated and treated with saturated aqueous sodium picrate. The solution and the precipitated picrate were heated in a boiling-water bath and filtered hot; cooling the filtrate gave **1-*methylquinolizinium picrate*** which on recrystallisation from absolute ethanol formed needles (2·4 g., 54% overall yield from the acetal), m. p. 149° (Found: C, 51·5; H, 3·1. $C_{16}H_{12}O_7N_4$ requires C, 51·6; H, 3·25%) $\lambda_{max.}$ 2290, 2920, 3190, 3320 ($\log_{10}$ ε 4·54, 3·77, 4·25, 4·48) in 95% ethanol. The ***perchlorate***, obtained by anionic exchange, crystallised from absolute ethanol–ethyl acetate as colourless needles, m. p. 168—169° (Found: C, 49·1; H, 4·2. $C_{16}H_{10}O_4NCl$ requires C, 49·3; H, 4·1%), $\lambda_{max.}$ 2290, 2890, 3160, 3300 Å ($\log_{10}$ ε 4·34, 3·61, 4·1, 4·29) in water.

4-*Ethoxy*-1-*phenyl*-1-2′-*pyridylbutan*-1-*ol* (XVIII; R = Ph).—A solution of 2-benzoylpyridine (10 g.) in anhydrous ether (50 ml.) was added slowly with stirring, under nitrogen, to the Grignard reagent from 3-ethoxypropyl bromide [10] (15 g.) in anhydrous ether (200 ml.). Worked up as for compound (XVIII; R = Me), the ***alcohol*** (11 g., 74%) had b. p. 140°/0·05 mm. (Found: C, 75·2; H, 8·1; N, 5·45. $C_{17}H_{21}O_2N$ requires C, 75·25; H, 7·8; N, 5·2%).

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UNIVERSITY COLLEGE OF N. STAFFS., KEELE, STAFFS. [*Received, January 1st*, 1959.]

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335. *The 11-Oxo- and 12-Oxo-derivatives of Cholest-4-en-3-one.*

By DAVID N. KIRK and VLADIMIR PETROW.

The compounds named in the title have been prepared by using deoxycholic acid as starting material.

THE 11-oxo- (II; R = O, R′ = H_2) and 12-oxo-derivative (II; R = H_2, R′ = O) of cholest-4-en-3-one were required for studies dealing with biogenesis. For their preparation deoxycholic acid was chosen as raw material, attention being first directed to cholestene-3 : 12-dione, as the intermediates therefrom seemed likely to prove of value in the production of the 11-oxygenated isomer.

Deoxycholic acid diformate [1] was converted into the acid chloride and thence by reaction with di*iso*propylcadmium [2] into 3α : 12α-dihydroxycoprostan-24-one (I; R = R″ = ···OH, −H; R′ = H_2), isolated as the crystalline 3-(hydrogen succinate). The constitution assigned to this ester was established by oxidation of the 12α-hydroxy-group followed by Huang-Minlon reduction [3] of the resulting dione; coprostan-3α-ol [4] was obtained.

Huang-Minlon reduction of the parent 3α : 12α-dihydroxycoprostan-24-one 3-(hydrogen succinate) gave coprostane-3α : 12α-diol (Ia; R = R″ = ···OH, −H; R′ = H_2), isolated as its crystalline 3α-(hydrogen succinate). Oxidation of the free diol with chromic acid furnished coprostane-3 : 12-dione (Ia; R = R″ = O, R′ = H_2), which passed readily on careful monobromination, followed by dehydrobromination, into the required cholest-4-ene-3 : 12-dione (II; R = H_2, R′ = O) [$\lambda_{max.}$ 240 mμ in $CHCl_3$; $\nu_{max.}$ 1710 (12-ketone), 1678 and 1620 cm.$^{-1}$ (4-en-3-one) [5]].

[1] Cortese and Bauman, *J. Biol. Chem.*, 1936, **113**, 779; Hoehn and Moffett, *J. Amer. Chem. Soc.*, 1945, **67**, 740.
[2] Riegel and Kaye, *J. Amer. Chem. Soc.*, 1944, **66**, 723; Kuwada and Yogo, *J. Pharm. Soc.* (*Japan*), 1937, **57**, 963.
[3] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487; 1949, **71**, 3301.
[4] Dorée and Gardner, *J.*, 1908, **93**, 1630; Dutcher and Wintersteiner, *J. Amer. Chem. Soc.*, 1939, **61**, 1992; Bridgewater and Shoppee, *J.*, 1953, 1709.
[5] Jones and Herling, *J. Org. Chem.*, 1954, **19**, 1252.

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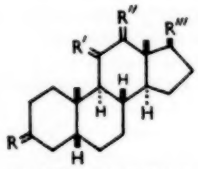
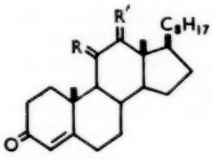
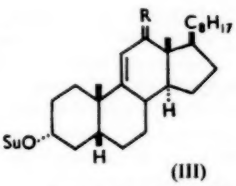
Conversion of coprostane-3α : 12α-diol 3-(hydrogen succinate) into an 11-oxygenated intermediate was unexpectedly difficult. Oxidation gave the 12-oxo-derivative, characterised by hydrolysis to amorphous 3α-hydroxycoprostan-12-one (Ia; R = ···OH, −H; R′ = H_2; R″ = O), which formed a crystalline acetate. Bromination of 12-oxocoprostan-3α-yl hydrogen succinate proceeded slowly in acetic acid at 70° to give two isomeric 11-bromo-derivatives. The major product, m. p. 149—152°, was shown to be the 11α-bromo-isomer (Ia; R = ···O·CO·$[CH_2]_2$·CO_2H, −H; R′ = ···Br, −H; R″ = O) by its stability



(I) R‴ = CHMe·CH_2·CH_2·$COPr^i$
(Ia) R‴ = C_8H_{17}



(II)



(III)
(Su = HO_2C·$[CH_2]_2$·CO-)

to boiling pyridine and by its ultraviolet absorption maximum at 287 mμ (equatorial bromine).[6] The minor product of the bromination, m. p. 214—215°, exhibited maximum ultraviolet absorption at 311 mμ and was dehydrobrominated by boiling pyridine to 12-oxocoprost-9(11)-en-3α-yl hydrogen succinate (III; R = O) ($\lambda_{max.}$ 239·5 mμ). It was therefore assigned the 11β-(axial)formulation [6] (Ia; R = ···O·CO·$[CH_2]_2$·CO_2H, −H; R′ = ···H, −Br; R″ = O). Attempts to convert these isomeric bromo-derivatives, or the mixture resulting from the bromination, into 3α : 12β-dihydroxycoprostan-11-one (Ia; R = ···OH, −H; R′ = O, R″ = ···H, −OH) (cf. Gallagher [7]) by vigorous alkaline hydrolysis, led to amorphous products from which a crystalline hydrogen succinate was ultimately obtained. This derivative, though not analytically pure, was probably the required 3α : 12β-dihydroxycoprostan-11-one 3-(hydrogen succinate). Its transformation into a 12-bromo-derivative by phosphorus tribromide under the conditions recommended by Hershberg *et al.*[8] led in very low yield to a product deficient in bromine which was not studied further.

No better results attended an attempt to extend to the 11-bromo-ketone the elegant procedure of Cornforth *et al.*[9] for converting hecogenin into 11-oxotigogenin. Thus reduction of the 11α-bromo-12-one with sodium borohydride led to a bromohydrin, but conversion of the latter into a crystalline 11β : 12β-epoxide could not be achieved with such reagents as alcoholic alkali [9] or silver oxide in pyridine.[10] Reduction of the bromohydrin with zinc dust [9] gave coprost-11-en-3-α-yl hydrogen succinate in very low yield, which was characterised as the dibromide.

One further route to the 11-ketone was examined. 12-Oxocoprostan-3α-yl hydrogen succinate (Ia; R = ···O·CO·$[CH_2]_2$·CO_2H, −H; R′ = H_2, R″ = O) was dehydrogenated with selenium dioxide in propionic acid to the 9(11)-dehydro-derivative (III; R = O), previously obtained from the 11β-bromo-12-one (cf. above). Huang-Minlon reduction followed by succinoylation furnished a very low yield of coprost-9(11)-en-3α-yl hydrogen succinate (III; R = H_2). Attempted addition of the elements of hypobromous acid to this compound employing *N*-bromoacetamide,[11] with or without added perchloric acid, failed to give a satisfactory product.

These discouraging results led us to examine an alternative route from deoxycholic acid

[6] Cookson, *J.*, 1954, 282.
[7] Gallagher, *J. Biol. Chem.*, 1946, **162**, 539; Borgstrom and Gallagher, *ibid.*, 1949, **177**, 951.
[8] Hershberg, Herzog, Coan, Weber, and Jevnik, *J. Amer. Chem. Soc.*, 1952, **74**, 2585.
[9] Cornforth, Osbond, and Phillipps, *J.*, 1954, 907.
[10] Schmidlin and Wettstein, *Helv. Chim. Acta*, 1953, **36**, 1241.
[11] Hicks and Wallis, *J. Biol. Chem.*, 1946, **162**, 641; Callow and James, *J.*, 1956, 4739.

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to cholest-4-ene-3 : 11-dione *via* 3α-hydroxy-11-oxocholan-24-oic acid.[7] The latter, after acetylation or formylation of the 3α-hydroxy-group, was treated with thionyl chloride. The resulting acid chloride with di*iso*propylcadmium gave 3α-hydroxycoprostane-11 : 24-dione (I; R = ···OH, −H; R′ = O; R″ = H_2). The 24-oxo-group was selectively eliminated therefrom by Huang-Minlon reduction, whch does not normally attack 11-ketones,[3] to give 3α-hydroxycoprostan-11-one (Ia; R = ···OH, −H; R′ = O; R″ = H_2). Mild oxidation furnished coprostane-3 : 11-dione (Ia; R = R′ = O, R″ = H_2), which passed into the 4-monobromo-derivative on careful bromination.[12] Reaction with ethoxycarbonylhydrazine,[13] followed by cleavage of the derived hydrazone with acetone and hydrochloric acid,[13] furnished the required cholest-4-ene-3 : 11-dione (II; R = O, R′ = H_2), which was characterised by its ultraviolet absorption maximum at 238·5 mμ, and by infrared absorption bands at 1706 (11-one) and 1676 cm.$^{-1}$ (4-en-3-one [5]).

Experimental

Optical rotations were measured in a 1 dm. tube in chloroform solution unless otherwise stated. Ultraviolet and infrared absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc. B.D.H. chromatographic alumina was used.

3α : 12α-*Dihydroxycoprostan*-24-*one* 3-(*Hydrogen Succinate*) (I; R = ···O·CO·$[CH_2]_2$·CO_2H, −H; R′ = H_2, R″ = ···OH, −H).—A solution of *iso*propylmagnesium bromide prepared from magnesium (27 g.), *iso*propyl bromide (106 ml.), and ether (300 ml.) was diluted with dry benzene (800 ml.), cooled to −10°, and treated under nitrogen with cadmium bromide (160 g.; freshly dried at 120°) in small portions during 45 min., at <5°. After a further 2 hours' stirring at −5° to 0° the solution was free from *iso*propylmagnesium bromide (Michler's ketone test [14]).

Deoxycholic acid diformate (50 g.) was treated with purified thionyl chloride (400 ml.) for 2 hr. at room temperature, then excess of thionyl chloride was removed under reduced pressure at 60°. Dry toluene (400 ml.) was added and distilled off under the same conditions, and the solid residue, dissolved in dry benzene (400 ml.), was added to the stirred solution of di*iso*propylcadmium at 0°. Next morning the mixture was poured into water (4 l.), concentrated hydrochloric acid (150 ml.), and crushed ice (1 kg.). The organic layer was washed, dried, and distilled to dryness, and the residue treated with potassium hydroxide (16 g.) in methanol (500 ml.) and water (30 ml.). The crude product, in benzene solution, was passed through a column of alumina (600 g.). Elution with ether and chloroform gave material (28·9 g.) which was treated with succinic anhydride (72 g.) in pyridine (300 ml.) for 1·5 hr. at 90°. The mixture was then stirred into water and after 2 hr. the product was extracted with ethyl acetate–benzene. Purification from ethyl acetate–hexane gave the *half-ester* as flakes, m. p. 136—137°, $[\alpha]_D^{24}$ +49° (*c* 0·5) (Found: C, 71·9; H, 9·8. $C_{31}H_{50}O_6$ requires C, 71·8; H, 9·7%).

Coprostan-3α-*ol*.—The foregoing compound (500 mg.) in acetic acid (20 ml.) was treated with potassium chromate (250 mg.) in water (5 ml.) at room temperature for 20 hr., to give the 12 : 24-dione 3-half-ester, leaflets (from ethyl acetate–hexane), m. p. 167—169°. This compound (400 mg.) and hydrazine hydrate (1 ml.) in diethylene glycol (20 ml.) were heated at 100° for ½ hr., then treated with hydrazine hydrate (0·5 ml.) and potassium hydroxide (2 g.) and the mixture was heated at 200° for 2 hr. in a stream of nitrogen, in an open flask. After the mixture had been poured into water, the product was isolated with ether–benzene, percolated through alumina (10 g.) in ether solution, and purified from methanol. Coprostan-3α-ol formed flakes, m. p. 117°, $[\alpha]_D^{22}$ +30° (*c* 0·18) (lit.,[4] m. p. 116—118°, $[\alpha]_D$ +30°).

The acetate separated from methanol as prisms, m. p. 86—87°, $[\alpha]_D^{22}$ +38° (*c*, 0·21) (lit.,[4] m. p. 83—84°).

Coprostane-3α : 12α-*diol* 3-(*Hydrogen Succinate*) (Ia; R = ···O·CO·$[CH_2]_2$·CO_2H, −H; R′ = H_2; R″ = ···OH, −H).—3α : 12α-Dihydroxycoprostan-24-one 3-(hydrogen succinate) (5·18 g.) and hydrazine hydrate (2·5 ml.) in diethylene glycol (50 ml.) were heated at 100° for ½ hr., then potassium hydroxide (6 g.) was added, and the mixture heated slowly to 200° in a stream of nitrogen in an open flask. After 2 hr. at 200° ± 5° the mixture was poured into dilute

[12] Koechlin, Kritchevsky, and Gallagher, *J. Biol. Chem.*, 1950, **184**, 393; Djerassi and Rosenkranz, *Experientia*, 1951, **7**, 93.
[13] Joly and Nominé, *Bull. Soc. chim. France*, 1956, 1381.
[14] Gilman and Schulze, *J. Amer. Chem. Soc.*, 1925, **47**, 2002.

hydrochloric acid and the product isolated by means of chloroform as a gum. This was treated with succinic anhydride (10 g.) in pyridine (40 ml.) at 90—100° for 1 hr. *Coprostane*-3α : 12α-*diol* 3-(*hydrogen succinate*), isolated with chloroform and purified from ether–hexane, formed flakes, m. p. 150—151°, $[\alpha]_D^{22}$ +48° (*c* 0·51) (Found: C, 73·6; H, 10·3. $C_{31}H_{52}O_5$ requires C, 73·7; H, 10·4%).

The free 3α : 12α-diol, obtained by hydrolysis of the ester, was isolated only as a powder, m. p. 80—100° with frothing (from aqueous acetone).

Coprostane-3 : 12-*dione* (Ia; R = R″ = O, R′ = H_2).—The foregoing crude diol (1·4 g.) in acetic acid (20 ml.) was treated with chromium trioxide (0·7 g.) in water (2 ml.) for 20 hr. at room temperature. Dilution with water gave a crystalline product which was purified from ethanol. *Coprostane*-3 : 12-*dione* formed plates, m. p. 138—138·5°, $[\alpha]_D^{23}$ +99° (*c* 0·22) (Found: C, 80·8; H, 11·0. $C_{27}H_{44}O_2$ requires C, 80·9; H, 11·1%).

4-*Bromocoprostane*-3 : 12-*dione*.—The dione (720 mg.) in acetic acid (15 ml.) was treated dropwise with bromine in acetic acid (1·0 mol.), then poured into water. Extraction with ether–benzene and purification from ethanol gave the 4-*bromo-dione* as flakes, m. p. 191—193°, $[\alpha]_D^{23}$ +135° (*c* 0·13) (Found: C, 67·8; H, 9·1; Br, 16·7. $C_{27}H_{43}O_2Br$ requires C, 67·6; H, 9·0; Br, 16·7%).

Cholest-4-*ene*-3 : 12-*dione* (II; R = H_2, R′ = O).—The 4-bromo-dione (480 mg.) in acetic acid (10 ml.) was treated with semicarbazide hydrochloride (390 mg.) and sodium acetate (300 mg.) in water (1 ml.) and acetic acid (10 ml.) under nitrogen, at 50° for 3 hr. *p*-Hydroxybenzaldehyde (3·9 g.) and sodium acetate (300 mg.) in 50% aqueous acetic acid (20 ml.) were added. After a further 3 hr. at 50° the mixture was poured into water, and the product extracted with ether, which was washed with sodium hydroxide solution until colourless, then with water, dried, and evaporated. Purification of the residue from methanol gave *cholest*-4-*ene*-3 : 12-*dione* as prisms, m. p. 117—118°, $[\alpha]_D^{23}$ +119° (*c* 0·28), $\lambda_{max.}$ 240 mμ (ε 15,150) in ethanol, $\nu_{max.}$ 1710, 1678, and 1620 cm.$^{-1}$ in carbon tetrachloride (Found: C, 81·2; H, 10·7. $C_{27}H_{42}O_2$ requires C, 81·3; H, 10·6%). The 3-(2 : 4-*dinitrophenylhydrazone*) separated from ethanol–chloroform in orange-red leaflets, m. p. 244—246°, $\lambda_{max.}$ 389 mμ (ε = 33,200) in chloroform (Found: N, 9·9. $C_{33}H_{46}O_5N_4$ requires N, 9·7%).

12-*Oxocoprostan*-3α-*yl Hydrogen Succinate* (Ia; R = ···O·CO·$[CH_2]_2$·CO_2H, −H; R′ = H_2, R″ = O).—Coprostane-3α : 12α-diol 3-(hydrogen succinate) (4·4 g.) in acetic acid (220 ml.) was treated with potassium chromate (2·2 g.) in water (22 ml.) at room temperature for 16 hr. The solids which separated proved difficult to filter, so water and chloroform were added, and the chloroform layer was washed neutral, dried and evaporated. The 12-*ketone* crystallised from methanol in flakes, m. p. 200—201°, $[\alpha]_D^{25}$ +92° (*c*, 0·37) (Found: C, 73·9; H, 10·0. $C_{31}H_{50}O_5$ requires C, 74·1; H, 10·0%).

The 3α-*acetate* was obtained after hydrolysis of the foregoing compound with aqueous methanolic potassium carbonate, and acetylation of the resulting amorphous hydroxy-ketone with acetic anhydride and pyridine. It separated from methanol in plates, m. p. 144—145°, $[\alpha]_D^{17}$ +117° (*c*, 0·45) (Found: C, 78·6; H, 10·8. $C_{29}H_{48}O_3$ requires C, 78·3; H, 10·9%).

Bromination of 12-*Oxocoprostan*-3α-*yl Hydrogen Succinate*.—The 12-ketone (10 g.) in acetic acid (100 ml.) at 70° was treated with bromine in acetic acid (19·0 ml. of 1·06M-solution). Decolorisation was completed in 1·5 hr.; then the solution was poured into water and the product isolated with chloroform. Crystallisation of the resulting material from acetone–hexane gave pale yellow crystals (2·25 g.), m. p. 183—192° (decomp.), which after purification from methanol gave 11β-*bromo*-12-*oxocoprostan*-3α-*yl hydrogen succinate* as flakes, m. p. 214—215° (decomp.), $[\alpha]_D^{16}$ +45° (*c*, 0·28), $\lambda_{max.}$ 311 mμ (ε 105) in ethanol (Found: C, 63·9; H, 8·4; Br, 14·1. $C_{31}H_{49}O_5Br$ requires C, 64·0; H, 8·5; Br, 13·7%).

The mother-liquors after crystallisation of the 11β-bromo-compound were evaporated to dryness, and the residue dissolved in aqueous methanol. The crystals which separated (7·94 g.; m. p. 138—147°) were purified from the same solvent to give the 11α-*bromo-ketone* in flakes, m. p. 150—154° (decomp.), $[\alpha]_D^{16}$ +59° (*c* 0·34), $\lambda_{max.}$ 287 mμ (ε 76) in ethanol (Found: C, 64·5; H, 8·7; Br, 13·1. $C_{31}H_{49}O_5Br$ requires C, 64·0; H, 8·5; Br, 13·7%).

Dehydrobromination of the 11β-*Bromo-ketone*.—The 11β-bromo-ketone (780 mg.) in pyridine (10 ml.) was heated under reflux for 2 hr. The product was isolated with chloroform and purified from methanol, giving 12-*oxocoprost*-9(11)-*en*-3α-*yl hydrogen succinate* (III; R = :O) as plates, m. p. 211—212°, $[\alpha]_D^{24}$ +50° (*c* 0·27), $\lambda_{max.}$ 239·5 mμ (ε 9460) in ethanol (Found: C, 74·4; H, 9·8. $C_{31}H_{48}O_5$ requires C, 74·3; H, 9·8%).

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The 11α-bromo-ketone was unaffected under the above conditions.

Alkaline Hydrolysis of 11(α + β)-Bromo-12-oxocoprostan-3α-yl Hydrogen Succinate.—The total product obtained by bromination of the 12-ketone (10 g.) as described above was heated under reflux in ethanol (200 ml.) with potassium hydroxide (23 g.) and water (25 ml.), under nitrogen for 6 hr. The product, isolated with chloroform, was a bromine-free oil. Esterification with succinic anhydride (10 g.) in pyridine (50 ml.) at 90° for ½ hr., isolation with chloroform, and crystallisation from aqueous methanol gave a product, m. p. 157—160°, $[\alpha]_D^{20}$ +31° (*c*, 0·31), which was probably impure 3α : 12β-dihydroxycoprostan-11-one 3-(hydrogen succinate) (Found: C, 73·0; H, 9·6. Calc. for $C_{31}H_{50}O_6$: C, 71·8; H, 9·7%).

11α-Bromocoprostane-3α : 12β-diol 3-(Hydrogen Succinate) (Ia; R = ···O·CO·$[CH_2]_2$·CO_2H, −H; R′ = ···Br, −H; R″ = ···H, −OH).—The 11α-bromo-ketone (5·81 g.) in methanol (400 ml.) was treated successively with sodium hydrogen carbonate (1·5 g.) in water (10 ml.), and sodium borohydride (1 g.) in ice-water (20 ml.). After 20 hr. at room temperature the solution was diluted with water. Extraction with ether and purification from aqueous methanol gave the *bromohydrin* in flakes, m. p. 135—138°, $[\alpha]_D^{17}$ +18° (*c* 0·33) (Found: C, 64·1; H, 8·9; Br, 13·5. $C_{31}H_{51}O_5Br$ requires C, 63·8; H, 8·8; Br, 13·7%).

Coprost-11-en-3α-yl Hydrogen Succinate.—The foregoing bromohydrin (2 g.) was stirred in boiling acetic acid (50 ml.) with zinc dust (4 g.) for 2 hr. The decanted solution was poured into water, and the product isolated with ether and purified from methanol. The *11-enyl ester* formed needles, m. p. 159—160°, $[\alpha]_D^{22}$ +125° (*c* 0·04) (Found: C, 76·3; H, 10·4. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·4%).

When this product (66 mg.) in carbon tetrachloride (10 ml.) was treated with an excess of bromine in carbon tetrachloride, the 11 : 12-*dibromide* was formed. After purification from methylene chloride–methanol it was obtained as a powder, m. p. 184—188° (decomp.), $[\alpha]_D^{25}$ +50° (*c* 0·23) (Found: C, 57·8; H, 7·6; Br, 24·9. $C_{31}H_{50}O_4Br_2$ requires C, 57·6; H, 7·8; Br, 24·7%).

Dehydrogenation of 12-Oxocoprostan-3-yl Hydrogen Succinate with Selenium Dioxide.—The 12-ketone (10 g.), selenium dioxide (2·6 g.), propionic acid (60 ml.), and 2N-hydrochloric acid (1 drop) were heated under reflux for 15 hr. The flakes which separated on cooling were purified from methanol–methylene chloride (selenium being removed by filtration). The keto-ester (III; R = O) formed plates, m. p. 211—212·5°, $[\alpha]_D^{25}$ +52° (*c* 0·24), $\lambda_{max.}$ 239·5 mμ (ε 9200) in ethanol, identical with the sample prepared from the 11β-bromo-ketone (above).

The propionic acid mother-liquors, after dilution with benzene, stirring for 1 hr. with a 25% aqueous solution of chromic acid to remove colloidal selenium,[15] evaporation, and crystallisation from methanol, yielded a further quantity of the same material.

Coprost-9(11)-en-3-yl Hydrogen Succinate (III; R = H_2).—Reduction of the last compound (7·5 g.) with hydrazine hydrate (4 ml.) in diethylene glycol (75 ml.) and potassium hydroxide (8 g.) by the general procedure described above, followed by re-succinoylation with succinic anhydride (10 g.) in pyridine (50 ml.) and purification from methanol, gave this *ester* (III; R = H_2) in fibrous needles, m. p. 149—151°, $[\alpha]_D^{23}$ +55° (*c* 0·27) (Found: C, 76·3; H, 10·2. $C_{31}H_{50}O_4$ requires C, 76·5; H, 10·4%).

3α-Formyloxy-11-oxocholan-24-oic Acid.—The 3α-hydroxy-acid (4·67 g.) in 98—99% formic acid (15 ml.) was heated at 75° for 3½ hr., then the formic acid was removed under reduced pressure, and the residue heated to 90° at 12—15 mm. pressure for ½ hr. Purification from 70% aqueous ethanol gave the *3-formate*, needles, m. p. 206°, $[\alpha]_D^{23}$ +68° (*c* 0·22 in methanol) (Found: C, 71·6; H, 9·2. $C_{25}H_{38}O_5$ requires C, 71·7; H, 9·2%).

3α-Hydroxycoprostane-11 : 24-dione (I; R = ···OH, −H; R′ = O; R″ = H_2).—A solution of di*iso*propylcadmium was prepared as described above from magnesium (2·95 g.), *iso*propyl bromide (12 ml.), ether (50 ml.), anhydrous benzene (100 ml.), and cadmium bromide (17 g.).

3α-Formyloxy-11-oxocholan-24-oic acid (3·2 g.) was treated with pure thionyl chloride (25 ml.) for 2 hr. at room temperature, then excess of thionyl chloride was removed under reduced pressure at 60°. Dry toluene (50 ml.) was added and distilled off under the same conditions, and the solid residue, dissolved in dry benzene (25 ml.), was added to the stirred solution of di*iso*propylcadmium at 0°. The mixture was left at room temperature overnight and poured into water (2 l.) containing acetic acid (150 ml.). The organic phase was washed, the solvent removed, and the residue treated with potassium hydroxide (0·5 g.) in 90% methanol (40 ml.) at 60° for ½ hr. The product was isolated by means of ether and benzene, the solvents

[15] McKenzie, Mattox, Engel, and Kendall, *J. Biol. Chem.*, 1948, **173**, 271.

were removed, and the residue (2·6 g.) in light petroleum (b. p. 40—60°) was chromatographed on to alumina (60 g.). Elution with benzene and purification from hexane gave *3α-hydroxycoprostane-11 : 24-dione* in needles, m. p. 114—116°, $[\alpha]_D^{22}$ +61° (*c* 0·50) (Found: C, 77·7; H, 10·9. $C_{27}H_{44}O_3$ requires C, 77·8; H, 10·7%).

The same product was obtained when the 3-acetate [16] was used in place of the formate.

3α-Benzoyloxycoprostane-11 : 24-dione formed flakes, m. p. 148—149°, $[\alpha]_D^{27}$ +70° (*c* 0·17) (Found: C, 78·7; H, 9·3. $C_{34}H_{48}O_4$ requires C, 78·5; H, 9·2%).

3α-Hydroxycoprostan-11-one (Ia; R = ···OH, −H; R′ = O; R″ = H_2).—3α-Hydroxycoprostane-11 : 24-dione (1·5 g.) in diethylene glycol (30 ml.) containing 100% hydrazine hydrate (1 ml.) was heated at 100° for ½ hr., then solid potassium hydroxide (3 g.) was added. The mixture was heated in an open flask in a stream of nitrogen for 2 hr. at 200—205°, then cooled and poured into dilute hydrochloric acid. The product, isolated by means of ether, failed to crystallise even after percolation through alumina. Esterification with *p*-nitrobenzoyl chloride in pyridine gave *3α-p-nitrobenzoyloxycoprostane-11-one* which crystallised from ethanol–acetone in leaflets, m. p. 121°, $[\alpha]_D^{20}$ +74° (*c* 0·10) (Found: C, 73·9; H, 8·9; N, 2·8. $C_{34}H_{49}O_5N$ requires C, 74·0; H, 8·9; N, 2·5%).

Hydrolysis of the *p*-nitrobenzoate with aqueous-methanolic potassium hydroxide (2 hr. under reflux) gave *3α-hydroxycoprostan-11-one*, leaflets (from aqueous methanol), m. p. 115—116°, $[\alpha]_D^{23}$ +62° (*c* 0·21) (Found: C, 80·2; H, 11·4. $C_{27}H_{46}O_2$ requires C, 80·4; H, 11·5%).

Coprostane-3 : 11-dione (Ia; R = R′ = O, R″ = H).—The foregoing compound (435 mg.) in acetic acid (20 ml.) was treated with chromium trioxide (200 mg.) in water (1 ml.) and acetic acid (3 ml.) for 16 hr. at room temperature, then poured into water. *Coprostane-3 : 11-dione*, isolated with ether, separated from hexane in prisms, m. p. 118°, $[\alpha]_D^{23}$ +57·5° (*c* 0·18) (Found: C, 80·6; H, 11·4. $C_{27}H_{44}O_2$ requires C, 80·9; H, 11·1%).

The *3-(mono-2 : 4-dinitrophenylhydrazone)* separated from ethyl acetate in yellow plates, m. p. 187—188° (Found: N, 10·1. $C_{33}H_{48}O_5N_4$ requires N, 9·6%).

4-Bromocoprostane-3 : 11-dione.—Coprostane-3 : 11-dione (670 mg.) in acetic acid (10 ml.) was treated dropwise with bromine in acetic acid (9·0 ml. of 0·187M-solution). After 20 min. the solution was diluted with water to turbidity, and the solids which separated were purified from hexane. The *4-bromo-dione* formed prisms, m. p. 143—144°, $[\alpha]_D^{24}$ +123° (*c* 0·07) (Found: C, 67·1; H, 9·3; Br, 16·2. $C_{27}H_{43}O_2Br$ requires C, 67·6; H, 9·0; Br, 16·7%).

Cholest-4-ene-3 : 11-dione (II; R = O, R′ = H_2).—The 4-bromo-dione (400 mg.) and ethoxycarbonylhydrazine (240 mg.) in acetic acid (5 ml.) were heated on the steam-bath for 15 min., then acetone (35 ml.) and concentrated hydrochloric acid (10 ml.) were added and the mixture was allowed to cool. The solids which separated on dilution of the solution with water were purified from aqueous methanol, then from hexane. *Cholest-4-ene-3 : 11-dione* formed rectangular prisms, m. p. 107—109°, $[\alpha]_D^{29}$ +173° (*c* 0·10), $\lambda_{max.}$ 238·5 mμ (ε 13,630) in ethanol, $\nu_{max.}$ 1706 (satd. C=O), 1676 (αβ-unsatd. C=O), and 1616 cm.$^{-1}$ (conjugated C=C) in carbon disulphide (Found: C, 81·0; H, 10·4. $C_{27}H_{42}O_2$ requires C, 81·3; H, 10·6%).

The *2 : 4-dinitrophenylhydrazone* separated from ethanol as an orange-red powder, m. p. 198—200°, $\lambda_{max.}$ 386·5 mμ (ε 29,800) in chloroform (Found: N, 10·1. $C_{33}H_{46}O_5N_4$ requires N, 9·7%).

We thank the Directors of The British Drug Houses Ltd. for permission to publish these results.

THE BRITISH DRUG HOUSES LTD.,
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[16] Turner, Mattox, Engel, McKenzie, and Kendall, *J. Biol. Chem.*, 1946, **166**, 345.

336. *The Structure of* Acacia pycnantha *Gum.*

By G. O. Aspinall, E. L. Hirst, and A. Nicolson.

Controlled acid-hydrolysis of the gum liberates L-arabinose and L-rhamnose with the formation of a degraded gum containing residues of D-galactose and D-glucuronic acid. 3-*O*-L-Arabofuranosyl-L-arabinose has been isolated during the early stages of the hydrolysis. Partial acid-hydrolysis of the fragment remaining after degradation of the periodate-oxidised degraded gum with phenylhydrazine affords 3-*O*-β-D-galactopyranosyl-D-galactose and only small amounts of a second disaccharide. Hydrolysis of the methylated degraded gum yields 2 : 3 : 4 : 6-tetra-, 2 : 4 : 6-tri-, 2 : 4- and 2 : 6-di-, and 2-*O*-methyl-D-galactose, (2 : 3 : 4-tri-*O*-methyl-6-D-galactopyranose 2 : 3 : 4-tri-*O*-methyl-β-D-glucopyranosid)uronic acid, and traces of other sugars. Hydrolysis of the methylated gum affords 2 : 3 : 5-tri- and 2 : 5-di-*O*-methyl-L-arabinose, 2 : 3 : 4 : 6-tetra-, 2 : 3 : 4- and 2 : 4 : 6-tri-, 2 : 4- and 2 : 6-di-, and 2-*O*-methyl-D-galactose, 2 : 3 : 4-tri-*O*-methyl-L-rhamnose, (2 : 3 : 4-tri-*O*-methyl-6-D-galactopyranose 2 : 3 : 4-tri-*O*-methyl-β-D-glucopyranosid)uronic acid, and traces of other sugars. It is concluded that the gum is a highly branched polysaccharide containing a framework of D-galactopyranose residues with main chains linked 1 ⟶ 3 and with side-chains attached by 1 ⟶ 6 linkages; to this branched framework are attached side-chains of L-rhamnopyranose, L-arabofuranose, 3-*O*-L-arabofuranosyl-L-arabofuranose, and (6-D-galactopyranose β-D-glucopyranosid)uronic acid residues. The structure of the gum is compared with that of gum arabic.

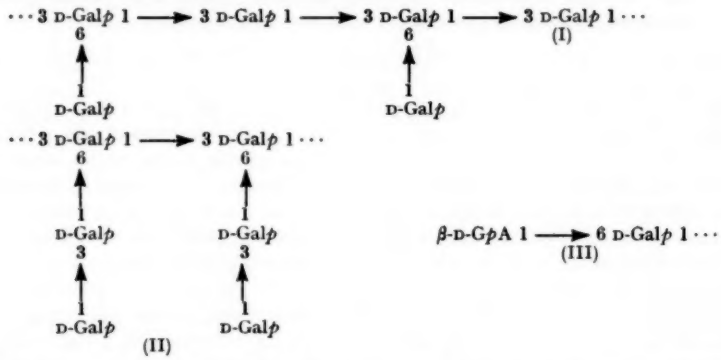
A previous investigation [1] of *Acacia pycnantha* gum showed that the gum is composed of residues of D-galactose (65%), L-arabinose (27%), L-rhamnose (1—2%), and D-glucuronic acid (5%). Although containing the same sugar units, the gum differs considerably from gum arabic [2,3] and the gums from other *Acacia* species [4] in the proportions of the constituent sugars. The gum is similar to these gums in giving rise to the aldobiouronic acid (6-D-galactose β-D-glucopyranosid)uronic acid, as a product of partial acid-hydrolysis. A further similarity with gum arabic is the formation of 3-*O*-β-D-galactopyranosyl-D-galactose as another product of partial acid hydrolysis. In this paper the results of further structural investigations on *A. pycnantha* gum are reported and in consequence a more detailed comparison of the structure of the gum with that of gum arabic is possible.

Hydrolysis of the gum under controlled conditions resulted in the release of arabinose and rhamnose, and only traces of galactose, with the formation of a stable degraded gum virtually free from arabinose residues. When the mild hydrolysis was arrested at an early stage an arabinose-containing disaccharide was present amongst the products. A quantity of this material was isolated by chromatography on cellulose; it had chromatographic mobility and optical rotation ($[\alpha]_D$ +89°) similar to those reported for 3-*O*-L-arabofuranosyl-L-arabinose isolated from sugar-beet araban.[5] Since the disaccharide was readily hydrolysed by acid it probably contained a furanosyl linkage, and its absence at later stages in the hydrolysis of the gum indicated that it was not an acid reversion product.[6] The presence of a 3-*O*-substituted arabinose residue was indicated by the formation of *ca.* 1 mol. of formaldehyde on periodate oxidation of the disaccharide and of 1·54 mols. of formaldehyde on similar oxidation of the derived glycitol.[7] Confirmation of the structure of the

[1] Hirst and Perlin, *J.*, 1954, 2622; Perlin, *Analyt. Chem.*, 1955, **27**, 396.
[2] Smith, *J.*, 1939, 744, 1724; 1940, 1035; Jackson and Smith, *J.*, 1940, 74, 79.
[3] Smith and Spriestersbach, Amer. Chem. Soc. Meeting, Minneapolis, Sept., 1955, Abs. Papers, 15D; Dillon, O'Ceallachain, and O'Colla, *Proc. Roy. Irish Acad.*, 1953, **55**, *B*, 331; 1954, **57**, *B*, 31.
[4] Stephen, *J.*, 1951, 646; Charlson, Nunn, and Stephen, *J.*, 1955, 269, 1428; Hulyachar, Ingle, and Bhide, *J. Indian Chem. Soc.*, 1956, **33**, 861; Mukherjee and Shrivastava, *J. Amer. Chem. Soc.*, 1958, **80**, 2536.
[5] Andrews, Hough, and Powell, *Chem. and Ind.*, 1956, 658.
[6] Jones and Nicholson, *J.*, 1958, 27.
[7] Hough, Woods, and Perry, *Chem. and Ind.*, 1957, 1100.

disaccharide as 3-*O*-L-arabofuranosyl-L-arabinose was obtained by the isolation of 2 : 3 : 5-tri- and a mixture of 2 : 4- and 2 : 5-di-*O*-methyl-L-arabinose on hydrolysis of the methylated disaccharide.

The degraded gum was converted into the fully methylated derivative, hydrolysis of which afforded 2 : 3 : 4 : 6-tetra-, 2 : 4 : 6-tri-, and 2 : 4-di-*O*-methyl-D-galactose, and a methylated aldobiouronic acid, together with smaller amounts of 2 : 6-di- and 2-*O*-methyl-D-galactose. Very small amounts of 2 : 3 : 4-tri-*O*-methyl-D-galactose and 2 : 3-di-*O*-methyl-L-arabinose were probably also present in the hydrolysate. The methylated aldobiouronic acid was shown to be (2 : 3 : 4-tri-*O*-methyl-6-D-galactopyranose 2 : 3 : 4-tri-*O*-methyl-β-D-glucopyranosid)uronic acid since reduction of the derived methyl ester methyl glycoside with lithium aluminium hydride followed by hydrolysis yielded 2 : 3 : 4-tri-*O*-methyl-D-glucose and 2 : 3 : 4-tri-*O*-methyl-D-galactose. It follows from the isolation from the methylated degraded gum of 2 : 3 : 4 : 6-tetra-, 2 : 4 : 6-tri-, and 2 : 4-di-*O*-methyl-D-galactose in approximately equimolecular amounts that the degraded gum contains a highly branched stable framework of 1 : 3- and 1 : 6-linked D-galactopyranose residues, for which partial structures (I), (II), and other variants may be advanced. The isolation of the fully etherified aldobiouronic acid, (2 : 3 : 4-tri-*O*-methyl-6-D-galactopyranose 2 : 3 : 4-tri-*O*-methyl-β-D-glucopyranosid)uronic acid, indicates that aldobiouronic acid units (III) must be attached as side-chains to the galactan backbone, but there is no evidence yet for the positions of linkage of these units. It is not yet known if the minor products of hydrolysis of this methylated polysaccharide are of structural significance.



Evidence in favour of structure (I) for the major part of the degraded gum was obtained by application of Barry's method of degradation [8] to the polysaccharide. Periodate-oxidised degraded gum was treated with phenylhydrazine and partial acid hydrolysis of the residual polymer afforded 3-*O*-β-D-galactopyranosyl-D-galactose as the main disaccharide product with only traces of the 1 : 6-linked isomer being detected chromatographically. It follows that the main chain is composed essentially of 1 : 3-linked β-D-galactopyranose residues as required by structure (I) and that the 1 : 6-linkages in the degraded gum are those of D-galactose residues attached as side-chains. The isolation of a small amount of a 1 : 3-linked galactotriose and higher homologues provides further evidence in support of this structure. The 1 : 3- and 1 : 6-linked D-galactopyranose residues in *Acacia pycnantha* gum are, therefore, similarly arranged to those in gum arabic [3] and in larch ε-galactan.[9]

The characteristic linkages of the sugar residues in the undegraded gum were established by analysis of the complex mixture of methylated sugars obtained on hydrolysis of the methylated gum. The following sugars were characterised by the formation of crystalline

[8] Barry and Mitchell, *J.*, 1954, 4020.
[9] Aspinall, Hirst, and Ramstad, *J.*, 1958, 593.

derivatives: 2 : 3 : 5-tri- and 2 : 5-di-*O*-methyl-L-arabinose, 2 : 3 : 4-tri-*O*-methyl-L-rhamnose, 2 : 3 : 4 : 6-tetra-, 2 : 3 : 4- and 2 : 4 : 6-tri-, and 2 : 4-di-*O*-methyl-D-galactose, and the methylated aldobiouronic acid, (2 : 3 : 4-tri-*O*-methyl-6-D-galactopyranose 2 : 3 : 4-tri-*O*-methyl-β-D-glucopyranosid)uronic acid. In addition small amounts of 2 : 6-di- and 2-*O*-methyl-D-galactose were identified, and two unidentified dimethyl ethers of arabinose (probably the 3 : 5- and 2 : 3-isomers) were also present. These sugars were not present in sufficient quantity to be considered as major structural units and some, indeed, may be products of incomplete methylation.

The significance of these results may be assessed by comparing the nature and amounts of the various methylated sugars isolated from the methylated derivatives of the degraded and undegraded gums. Taking the galactan structure (I) with attached aldobiouronic acid units (III) as a working model for the degraded gum, we may consider first the nature of the acid-labile residues removed during the mild acid-hydrolysis, and, secondly, the points of attachment of these groups to the galactan framework. The isolation of the same fully etherified aldobiouronic acid from methylated degraded and undegraded gums indicates that no substituents are linked to the acidic disaccharide units (III).

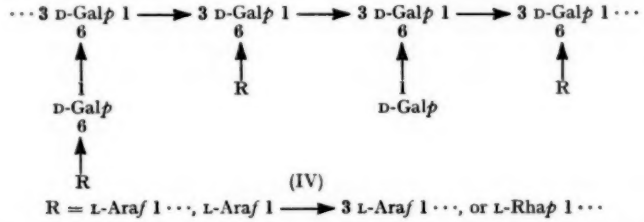
The only L-rhamnose derivative found on hydrolysis of the methylated gum was the 2 : 3 : 4-trimethyl ether, therefore the small proportions of these sugar residues in the gum occur solely as end groups in the pyranose form. Apart from traces of arabinose residues giving rise to 2 : 3-di-*O*-methylarabinose and which may be present in either furanose or pyranose form, L-arabinose residues in the gum occur solely in the furanose form, approximately two-thirds in terminal and one-third in non-terminal positions linked 1 ⟶ 3. Since 3-*O*-L-arabofuranosyl-L-arabinose has been identified as a partial acid hydrolysis product of the gum, the simplest, but not the only, assignment of arabinose residues is of equal proportions of single L-arabofuranose and of 3-*O*-L-arabofuranosyl-L-arabofuranose residues attached as side chains to the galactan framework. The points of attachment of the acid-labile residues to galactose residues in the gum follow from a comparison of the proportions of D-galactose methyl ethers formed on hydrolysis of the methylated gum and of the methylated degraded gum. In the absence of galactose and galactose-containing oligosaccharides amongst the low-molecular-weight products of mild acid hydrolysis of the gum it may be assumed that the galactan framework of the gum is substantially undisturbed during the formation of the degraded gum. The most striking difference is the large increase in the proportion of 2 : 4 : 6-tri-*O*-methyl-D-galactose from the methylated degraded gum and the corresponding decrease in the proportion of 2 : 4-di-*O*-methyl-D-galactose. It follows that a large proportion of the acid-labile groups are attached to position 6 of 1 ⟶ 3 linked D-galactopyranose residues in the main chains of the molecular structure. A second but significant difference is the increase in the proportion of 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose which corresponds approximately with the decrease in the proportion of 2 : 3 : 4-tri-*O*-methyl-D-galactose. Further acid-labile groups are therefore linked to position 6 of D-galactopyranose residues present as side chains in the gum. It is not possible to ascribe particular points of attachment to the various types of acid-labile groups, but on the basis of present knowledge the main structural features of *Acacia pycnantha* gum may be summarised in structure (IV), with aldobiouronic acid units (III) attached in a manner as yet unknown.

Sufficient is now known of the mode and order of linkage of the constituent sugar residues of *Acacia pycnantha* gum for a broad comparison of its structure to be made with that of gum arabic. The structure (V) for gum arabic is based upon the classic work of Smith [2] and upon more recent investigations [3] in which the presence of the backbone of 1 : 3-linked galactose residues has been established.

The two gums contain highly branched backbones of galactose residues in which the main chain is linked 1 ⟶ 3 and side-chains are attached by 1 ⟶ 6 linkages, but whereas all the galactose residues in the main chain of gum arabic carry galactose-containing side-chains, such side-chains are attached only to every second galactose residue in the main

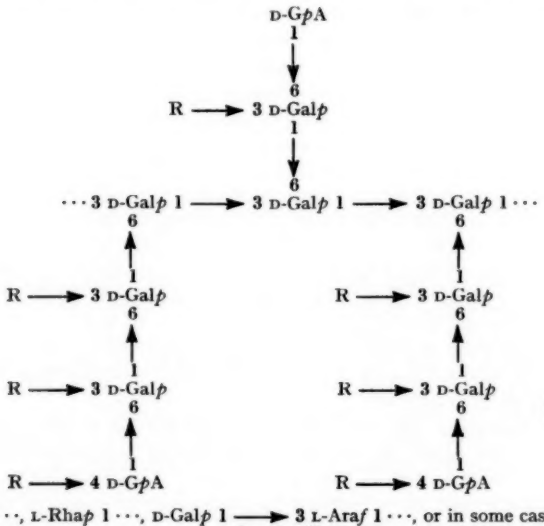
Proportions of methyl ethers of D-*galactose.*

Methyl ether	Hydrolysis of methylated gum	Hydrolysis of methylated degraded gum	Difference
2 : 3 : 4 : 6-Tetra-	1·0	1·6	+0·6
2 : 3 : 4-Tri-	0·65	0·25	−0·4
2 : 4 : 6-Tri-	0·2	1·7	+1·5
2 : 4-Di-	3·4	1·4	−2·0



R = L-Araf 1 ···, L-Araf 1 → 3 L-Araf 1 ···, or L-Rhap 1 ···

chain of *Acacia pycnantha* gum. Both gums contain the same aldobiouronic acid units in the side-chains of the molecule but the precise mode of attachment to the backbone in the latter case is not known. Similarities between the two gums are also shown by the L-arabofuranose and L-rhamnopyranose end groups which are removed by mild acid hydrolysis. The gums differ, however, in the nature of the more complex side-chains also removed under these conditions. In gum arabic these are 3-*O*-D-galactopyranosyl-L-arabofuranose and in some cases [10] 3-*O*-L-arabopyranosyl-L-arabofuranose groups, but in *A. pycnantha* gum they are 3-*O*-L-arabofuranosyl-L-arabofuranose groups. It may be noted, however, that in both cases the non-terminal L-arabofuranose residues carry substituents at position 3. The most marked differences between the two gums are shown in the positions of linkage to galactose or glucuronic acid residues of the various groups on the periphery of the gum



R = L-Araf 1 ···, L-Rhap 1 ···, D-Galp 1 → 3 L-Araf 1 ···, or in some cases [10] L-Arap 1 → 3 L-Araf 1 ···

structure. Although it is not known to which positions specific groups are attached, in gum arabic they are linked to $C_{(3)}$ of galactose residues in the outer chains and to $C_{(4)}$ of

[10] Andrews and Jones, *J.*, 1955, 583.

glucuronic acid residues, whereas in *Acacia pycnantha* gum they are linked to $C_{(6)}$ of galactose residues in both the main and outer chains.

In the absence of any strict proof of homogeneity caution must be exercised in the interpretation of the results of structural investigations of complex polysaccharides such as the plant gums. There is indeed evidence for a measure of heterogeneity in some samples of gum arabic [11,12] and of other *Acacia* gums [12] including *A. pycnantha* gum. Professor F. Smith (personal communication) informs us that glass-fibre paper ionophoresis in 2N-sodium hydroxide shows his sample of *Acacia pycnantha* gum to contain a major and a minor component. Glass-fibre paper ionophoresis of the gum sample used by us showed only one component, although another sample of the gum showed a similar degree of heterogeneity to that examined by Professor Smith. There is however no detailed information regarding the nature of the heterogeneity and it is not possible therefore to state whether different fractions from a single gum consist of similarly constituted polysaccharides differing only in some minor respect, or whether there are more fundamental differences of structure. Nevertheless, it is already clear from the comparisons made that the major components of the two gums have important structural features in common. It is indeed possible that just as many polysaccharides of the hemicellulose groups have been shown to be members of the same general family but differing considerably in fine structure,[13] so the vastly more complicated gums from related botanical species may be shown to contain similar basal units of molecular structure upon which are superimposed even wider variations in detailed structure.

Experimental

Paper chromatography was carried out on Whatman No. 1 filter paper with the following solvent systems (v/v): (A) ethyl acetate–pyridine–water (10 : 4 : 3); (B) butan-1-ol–ethanol–water (4 : 1 : 5, upper layer); (C) ethyl acetate–acetic acid–water (3 : 1 : 3, upper layer); (D) butan-2-one, half saturated with water; (E) butan-1-ol–benzene–pyridine–water (5 : 1 : 3 : 3, upper layer). Unless otherwise stated, chromatography of methylated sugars was carried out in solvent B, and R_G values refer to the rate of movement relative to 2 : 3 : 4 : 6-tetra-*O*-methyl-D-glucose in that solvent. Demethylations of methylated sugars were performed by the method of Hough, Jones, and Wadman.[14] Paper ionophoresis was in borate buffer at pH 10. Optical rotations were observed at 18° ± 2°.

The gum was prepared from crude nodules as described previously, and the sample of methylated gum was that prepared by Hirst and Perlin.[1]

Partial Acid Hydrolysis and Preparation of the Degraded Gum.—The gum (1 g.) was heated with 0·01N-sulphuric acid (100 ml.) at 100°. The optical rotation of the solution was observed every hour, and every two hours samples (5 ml.) were withdrawn, neutralised with barium carbonate, filtered, shaken with Amberlite resin IR–120(H) to remove barium ions, and poured into ethanol (3 vol.) to precipitate degraded gum. The supernatant liquor and the hydrolysate from the degraded gum were examined chromatographically in solvent A. The results showed that the arabinose was almost completely removed after 10 hr. and the rhamnose after 14 hr. (solution had $[\alpha]_D$ +39°); only small quantities of galactose were released. In a more careful search for oligosaccharides released during the mild acid-hydrolysis, samples were passed through charcoal–Celite columns (1 : 1; 5 g.). Elution with water removed most of the monosaccharides and elution with 15% ethanol removed an unknown sugar of R_{Gal} 1·4 in solvents C and D. This sugar was present in the hydrolysate after 1 hr., in decreased amount after 2 hr., and was no longer present after 4 hr. or at later stages in the hydrolysis.

The gum (29 g.) was heated at 100° with 0·01N-sulphuric acid (1·5 l.) for 14 hr. ($[\alpha]_D$ −8° ⟶ +38°). The cooled solution was neutralised with Amberlite resin IR–4B(OH), concentrated, and poured into ethanol (4 vol.) to give the degraded gum (15 g.), $[\alpha]_D$ +20° (*c.* 1·2 in H_2O) (Found: uronic anhydride, 6%).

Partial Acid Hydrolysis and Isolation of 3-O-L-*Arabofuranosyl*-L-*arabinose.*—Further examination of the products of mild acid hydrolysis of the gum showed that the unknown sugar of

[11] Heidelberger, Adams, and Dische, *J. Amer. Chem. Soc.*, 1956, **78**, 2853.
[12] Lewis and Smith, *J. Amer. Chem. Soc.*, 1957, **79**, 3929.
[13] Hirst, *J.*, 1955, 2974.
[14] Hough, Jones, and Wadman, *J.*, 1950, 1705.

R_{Gal} 1·4 was present in greatest amount after the gum had been heated with 0·01N-sulphuric acid at 85° for 4 hr. The gum (10 g.) was heated at 85° with 0·01N-sulphuric acid (300 ml.) for 4 hr., and the cooled solution was neutralised with Amberlite resin IR–4B(OH), concentrated, and poured into ethanol (3 vol.). The precipitated degraded polysaccharide was removed and the supernatant liquor was concentrated to a syrupy mixture of sugars (2·2 g.), chromatography of which showed arabinose and small quantities of rhamnose, galactose, and the sugar of R_{Gal} 1·4. The syrup was fractionated on cellulose (2·8 × 80 cm.) by use of solvent D to give three fractions. Fraction 1 (1·7 g.) contained arabinose and traces of rhamnose and the disaccharide (R_{Gal} 1·4). Fraction 2 (105 mg.) contained the disaccharide with traces (*ca.* 1%) of galactose and arabinose. Fraction 3 (70 mg.) contained the disaccharide, galactose, and unidentified oligosaccharides.

The disaccharide (fraction 2) had $[\alpha]_D$ +89° (*c* 1·0 in H_2O) and gave only arabinose on hydrolysis. Periodate oxidation [15] of a sample (10 mg.) gave 0·87 mol. of formaldehyde, identified as the dimedone compound, m. p. 189—190°. A second sample (10 mg.) in water (2 ml.) was reduced with potassium borohydride (20 mg.) for 16 hr., and oxidation with periodate afforded formaldehyde corresponding to 1·54 mol. per mol. of glycitol.

Methyl sulphate (2 ml.) and 40% aqueous sodium hydroxide (3 ml.) were added dropwise to the sugar (80 mg.) in water (8 ml.) at 0°. Further additions of methyl sulphate (2 × 12 ml. + 6 ml.) and 40% sodium hydroxide (2 × 22 ml. + 9 ml.) were made at room temperature and the reaction was completed by heating the solution on the boiling-water bath for 1 hr. The cooled mixture was extracted with chloroform for 16 hr. to give methylated disaccharide (80 mg.). Hydrolysis of a sample (3 mg.) gave 2 : 3 : 5-tri- and 2 : 5- and 2 : 4-di-*O*-methylarabinose, with only traces of products of incomplete methylation. Hydrolysis of the methylated disaccharide (77 mg.) with N-sulphuric acid at 100° for 4 hr., followed by neutralisation with barium carbonate and deionisation, gave a syrup (68 mg.) which was separated on filter sheets with solvent B, to give three fractions. Fraction *a* (20 mg.), R_G 0·98, was identified as 2 : 3 : 5-tri-*O*-methyl-L-arabinose by conversion into 2 : 3 : 5-tri-*O*-methyl-L-arabonamide, m. p. and mixed m. p. 132—133°. Fraction *b* (10 mg.), R_G 0·84, was characterised as 2 : 5-di-*O*-methyl-L-arabinose by conversion into aldonamide, m. p. and mixed m. p. 123—124°. Fraction *c* (14 mg.), R_G 0·65, was identified as 2 : 4-di-*O*-methyl-L-arabinose by conversion into the aniline derivative, m. p. and mixed m. p. 131°.

Preparation and Hydrolysis of Methylated Degraded Gum.—The degraded gum (10 g.) was methylated by successive additions of methyl sulphate and sodium hydroxide, and then with methyl iodide and silver oxide, to give methylated degraded gum (3·1 g.), $[\alpha]_D$ −35° (*c* 1·0 in $CHCl_3$) (Found: OMe, 45·0%). The methylated degraded gum (2·9 g.) was suspended in N-hydrochloric acid (300 ml.) at 40° for 8 days. The resulting solution was heated at 100° for 16 hr. (constant rotation), cooled, neutralised with silver carbonate, and, after removal of silver ions as silver sulphide, treated with barium carbonate and concentrated to a syrup (2·4 g.). The syrupy mixture of sugars was separated on cellulose (3·5 × 90 cm.) with light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3; later 1 : 1) saturated with water, and butan-1-ol partly saturated with water, as eluants, to give ten fractions, and a further fraction was obtained by elution of the cellulose with water.

Fraction 1. The syrup (40 mg.), $[\alpha]_D$ +44° (*c* 0·4 in H_2O), contained a mixture of 2 : 3 : 5-tri-*O*-methylarabinose (R_G 0·98), 2 : 3 : 4-tri-*O*-methylrhamnose (R_G (1·01), and 2 : 3 : 4 : 6-tetra-*O*-methylgalactose (R_G 0·89). Demethylation gave rhamnose, arabinose, and galactose.

Fraction 2. The chromatographically pure sugar (525 mg.), R_G 0·89, crystallised from ether–light petroleum and had m. p. and mixed m. p. 68° (with 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose) and $[\alpha]_D$ +140° ⟶ +117° (*c* 1·0 in H_2O) (Found: OMe, 52·2. Calc. for $C_{10}H_{20}O_6$: OMe, 52·5%). The aniline derivative had m. p. and mixed m. p. 194°.

Fraction 3. The syrup (56 mg.), $[\alpha]_D$ +90° (*c* 1·1 in H_2O), contained tetra-*O*-methylgalactose (R_G 0·89) and a small quantity of 2 : 5-di-*O*-methylarabinose. Demethylation gave galactose and arabinose. The major component was identified by conversion into 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-galactosylamine, m. p. 191°.

Fraction 4. Chromatography of the partly crystalline material (583 mg.), $[\alpha]_D$ +128° ⟶ +94° (*c* 0·61 in H_2O), showed 2 : 4 : 6- and/or 2 : 3 : 4-tri-*O*-methylgalactose. Recrystallisation from acetone–ether–light petroleum afforded 2 : 4 : 6-tri-*O*-methyl-D-galactose, m. p. and mixed m. p. 101° and $[\alpha]_D$ +120° ⟶ +90° (*c* 0·71 in H_2O) (Found: OMe, 41·8%. Calc. for

[15] Reeves, *J. Amer. Chem. Soc.*, 1941, **63**, 1476.

$C_9H_{18}O_6$: OMe, 41·9%) (aniline derivative, m. p. and mixed m. p. 167—168°). A sample (10 mg.) of the fraction in water (10 ml.) was reduced with potassium borohydride (20 mg.) for 16 hr., excess of hydride was destroyed by addition of acetic acid, *p*-hydroxybenzaldehyde (2—3 mg.) was added, and the solution was made up to a standard volume. Equal volumes of sodium metaperiodate–sodium hydrogen carbonate solution were added to aliquot parts of the reduced sugar solution, and the formaldehyde released was estimated colorimetrically by the method of O'Dea and Gibbons.[16] The formaldehyde formed corresponded to the presence of 8% of the 2 : 3 : 4-trimethyl ether in the fraction. Attempts to characterise the second sugar by fractional crystallisation of the aniline derivatives failed.

Fraction 5. Chromatrography of the syrup (134 mg.), $[\alpha]_D$ +103° (*c* 1·2 in H_2O) showed 2 : 4 : 6- and/or 2 : 3 : 4-tri-*O*-methylgalactose and 2 : 3-di-*O*-methylarabinose. Demethylation gave galactose and arabinose. Treatment of the syrup with aniline furnished the characteristic needles of 2 : 4 : 6-tri-*O*-methyl-*N*-phenyl-D-galactosylamine, m. p. and mixed m. p. 165—166°. Concentration of the mother-liquor yielded a mixture, m. p. 146°, of needles and plates (characteristic of 2 : 3 : 4-tri-*O*-methyl-*N*-phenyl-D-galactosylamine), but it was not possible to separate the two components. Periodate oxidation of the derived mixture of glycitols gave 0·45 mol. of formaldehyde. If the presence of 10% of di-*O*-methylarabinose in the fraction is assumed, the fraction contained 2 : 3 : 4- (35%) and 2 : 4 : 6-tri-*O*-methyl-D-galactose (55%).

Fraction 6. The sugar (56 mg.), R_G 0·54, after recrystallisation from chloroform–light petroleum had m. p. and mixed m. p. (with 2 : 6-di-*O*-methyl-D-galactose monohydrate) 98—99°, and $[\alpha]_D$ +52° ⟶ +82° (*c* 0·55 in H_2O) (Found: OMe, 27·0. Calc. for $C_9H_{18}O_6,H_2O$: OMe, 27·2%). The aniline derivative had m. p. and mixed m. p. 119°

Fraction 7. Chromatography of the fraction (223 mg.), $[\alpha]_D$ +105° ⟶ +86° (*c* 0·88 in H_2O), showed 2 : 4- and 2 : 6-di-*O*-methyl-D-galactose, R_G 0·47 and 0·54, in the approximate proportion of 5 : 1. Demethylation gave galactose. Recrystallisation from acetone containing 1% of water gave 2 : 4-di-*O*-methyl-D-galactose monohydrate, m. p. and mixed m. p. 101° (aniline derivative, m. p. and mixed m. p. 216—217°). Chromatography of the products of periodate oxidation [17] of the mother-liquor showed unchanged 2 : 4-di-*O*-methylgalactose and methoxymalondialdehyde (from the 2 : 6-dimethyl ether), but no products characteristic of the 2 : 3-dimethyl ether.

Fraction 8. The sugar (212 mg.), R_G 0·47, after recrystallisation from acetone containing 1% of water had m. p. and mixed m. p. (with 2 : 4-di-*O*-methyl-D-galactose monohydrate) 102° and $[\alpha]_D$ +123° ⟶ +85° (*c* 0·68 in H_2O) (aniline derivative, m. p. and mixed m. p. 218°).

Fraction 9. The syrup (47 mg.), $[\alpha]_D$ +83° (*c* 0·47 in H_2O), contained 2 : 4-di-*O*-methylgalactose (R_G 0·47) and a small amount of 2-*O*-methylgalactose (R_G 0·29). Demethylation gave galactose.

Fraction 10. The sugar (49 mg.), R_G 0·29 and $[\alpha]_D$ +63° ⟶ +82° (*c* 0·49 in H_2O), after recrystallisation from glacial acetic acid had m. p. and mixed m. p. (with 2-*O*-methyl-D-galactose) 148—149°.

Fraction 11. Removal of barium ions by treatment with Amberlite resin IR–120(H) followed by concentration gave a syrup (108 mg.), which was converted into the methyl ester methyl glycoside by refluxing it with methanolic 3% hydrogen chloride (40 ml.) for 6 hr. Lithium aluminium hydride in tetrahydrofuran was added slowly to a boiling solution of the ester glycoside in tetrahydrofuran, and the mixture was refluxed for 2 hr. Excess of hydride was destroyed by water, the mixture was taken to dryness, and the residue was exhaustively extracted with chloroform and acetone to give a syrup (85 mg.). Hydrolysis of the syrup with N-hydrochloric acid at 100° for 4 hr. gave a mixture of sugars (69 mg.) which was separated on cellulose (50 × 2 cm.) with light petroleum (b. p. 100—120°)–butan-1-ol, saturated with water to give fractions *a* (23 mg.) and *b* (28 mg.). Fraction *a* was characterised as 2 : 3 : 4-tri-*O*-methyl-D-glucose by conversion into the aniline derivative, m. p. and mixed m. p. 134°. Fraction *b*, $[\alpha]_D$ +116° (*c* 0·28 in H_2O), was characterised as 2 : 3 : 4-tri-*O*-methyl-D-galactose by conversion into the aniline derivative, m. p. and mixed m. p. 169°.

Degradation of Periodate-oxidised Degraded Gum with Phenylhydrazine.—Degraded gum (3·5 g.) was oxidised with sodium metaperiodate (8·5 g.) in water (100 ml.) for 48 hr. in the dark (complete oxidation). The solution was treated with lead acetate to remove iodate and periodate, and then with dilute sulphuric acid to precipitate excess of lead. The resulting solution

[16] O'Dea and Gibbons, *Biochem. J.*, 1953, **55**, 580.
[17] Lemieux and Bauer, *Canad. J. Chem.*, 1953, **31**, 814.

was heated with phenylhydrazine (17 ml.) and glacial acetic acid (10 ml.) at 100° for 5 hr. The cooled solution was repeatedly extracted with ether, made 0·2N with respect to sulphuric acid and heated at 100° for 40 min. to cleave phenylosazone residues. The cooled solution was neutralised with Amberlite resin IR–4B(OH), extracted with ether, concentrated to 50 ml., and poured into ethanol (150 ml.) to precipitate the polysaccharide residue (1·0 g.).

Small-scale experiments showed that hydrolysis of the degraded polysaccharide with 0·5N-sulphuric acid at 100° for 56 min. gave a solution with 50% of the reducing power obtained on prolonged hydrolysis. Chromatography of the hydrolysate after this period showed galactose and 3-*O*-galactopyranosylgalactose. The degraded polysaccharide (0·9 g.) was heated with 0·5N-sulphuric acid (75 ml.) at 100° for 1 hr. The cooled solution was neutralised with Amberlite resin IR–4B(OH), concentrated, and poured into ethanol (3 vol.). The precipitated degraded polysaccharide was rehydrolysed under the same conditions and combination of the soluble hydrolysates afforded a syrup (350 mg.). The syrup (350 mg.) was dissolved in water and poured on charcoal–Celite (1 : 1; 100 g.). Elution with water afforded galactose (212 mg.). Elution with water containing 5% of ethanol gave a syrup (31 mg.) containing 3-*O*-galactopyranosylgalactose (R_{Gal} 0·60 in solvent A) and a trace of 6-*O*-galactopyranosylgalactose (R_{Gal} 0·40). Recrystallisation from ethanol–water gave 3-*O*-D-galactopyranosyl-D-galactose, identified by m. p. and mixed m. p. 145—147° and by *X*-ray powder photography. Elution with water containing 10% of ethanol gave a syrup (7 mg.) containing a sugar with R_{Gal} 0·33 in solvent A and higher oligosaccharides. Partial acid-hydrolysis gave galactose and 3-*O*-galactopyranosylgalactose.

Hydrolysis of Methylated Gum and Separation of Methylated Sugars.—The methylated gum (6·0 g.) was refluxed with methanolic 4% hydrogen chloride (300 ml.) for 18 hr. (constant rotation). Methanol was removed under reduced pressure and the product was heated with 0·5N-hydrochloric acid (300 ml.) on the boiling-water bath for 14 hr. (constant rotation). The cooled solution was neutralised with silver carbonate, then filtered, silver was removed with hydrogen sulphide, and the filtrate was concentrated. Sugars were extracted from the residue with methanol, and the resulting syrup was dissolved in water, neutralised with barium carbonate, filtered, and concentrated to a syrup (5·1 g.). The syrupy mixture of sugars was separated on cellulose (90 × 3·5 cm.) with light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3; later, 1 : 1) saturated with water, and butan-1-ol partly saturated with water, as eluants, to give eleven fractions, and a further fraction was obtained by elution of the cellulose with water.

Fraction 1. Chromatography of the syrup (640 mg.) showed 2 : 3 : 4-tri-*O*-methylrhamnose (R_G 1·01) and 2 : 3 : 5-tri-*O*-methylarabinose (R_G 0·98). The optical rotation $[\alpha]_D$ −23° (*c* 0·64 in H_2O) of the syrup corresponded to that of a mixture of 2 : 3 : 4-tri-*O*-methyl-L-rhamnose ($[\alpha]_D$ +24°) and 2 : 3 : 5-tri-*O*-methyl-L-arabinose ($[\alpha]_D$ −37°) in the proportions of 23 : 77. Demethylation with hydriodic acid gave rhamnose and arabinose. A portion (360 mg.) of the syrup was fractionated on cellulose (50 × 2 cm.) with light petroleum (b. p. 100—120°)–butan-1-ol, saturated with water, to give four fractions. Fraction 1*a* (47 mg.), $[\alpha]_D$ +24° (*c* 0·4 in H_2O), was characterised as 2 : 3 : 4-tri-*O*-methyl-L-rhamnose (aniline derivative, m. p. and mixed m. p. 111°). Fraction 1*b* (232 mg.), $[\alpha]_D$ −28° (*c* 1·0 in H_2O), contained a mixture of 2 : 3 : 4-tri-*O*-methyl-L-rhamnose and 2 : 3 : 5-tri-*O*-methyl-L-arabinose. Fraction 1*c* (47 mg.), $[\alpha]_D$ −37° (*c* 0·47 in H_2O), was chromatographically pure 2 : 3 : 5-tri-*O*-methyl-L-arabinose and afforded 2 : 3 : 5-tri-*O*-methyl-L-arabonamide, m. p. and mixed m. p. 135—136°. Fraction 1*d* (7 mg.), $[\alpha]_D$ +100° (*c* 0·14 in H_2O), was 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (R_G 0·89) which had not been detected previously in the fraction.

Fraction 2. Chromatography of the syrup (717 mg.) showed two components, R_G 0·98 and 0·89, and the optical rotation {$[\alpha]_D$ +92° (*c* 0·71 in H_2O)} corresponded to that of a mixture of 2 : 3 : 5-tri-*O*-methyl-L-arabinose ($[\alpha]_D$ −37°) and 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose ($[\alpha]_D$ +117°) in the proportion of 16 : 84. The major component was identified by conversion into 2 : 3 : 4 : 6-tetra-*O*-methyl-*N*-phenyl-D-galactosylamine, m. p. and mixed m. p. 191°.

Fraction 3. Chromatography of the syrup (42 mg.), $[\alpha]_D$ +62° (*c* 0·41 in H_2O), showed 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (identified as the aniline derivative, m. p. and mixed m. p. 189°) and small amounts of 2 : 3 : 5-tri- and 2 : 5-di-*O*-methylarabinose.

Fraction 4. Chromatography of the syrup (276 mg.), $[\alpha]_D$ +4·5° (*c* 1·1 in H_2O), showed di-*O*-methylarabinose (R_G 0·84) and a small amount of tetra-*O*-methylgalactose (R_G 0·89). Demethylation gave arabinose and a small amount of galactose. Separation of a portion (160 mg.) on cellulose using light petroleum (b. p. 100—120°)–butan-1-ol (7 : 3), saturated with water,

gave two fractions. Fraction 4*a* (18 mg.) was 2 : 3 : 4 : 6-tetra-*O*-methyl-D-galactose (aniline derivative m. p. and mixed m. p. 190°). Chromatography of fraction 4*b* (122 mg.) showed one sugar (R_G 0·84), but ionophoresis showed 2 : 5-di-*O*-methylarabinose together with a small amount of 3 : 5-di-*O*-methyl-arabinose. Demethylation gave only arabinose. The major component was identified by conversion into 2 : 5-di-*O*-methyl-L-arabonamide, m. p. and mixed m. p. 125—126°.

Fraction 5. Chromatography of the syrup (237 mg.), $[\alpha]_D$ +113° (*c* 1·0 in H_2O), showed a tri-*O*-methylgalactose (R_G 0·73) (Found: OMe, 41·2. Calc. for $C_9H_{18}O_6$: OMe, 41·9%). Demethylation gave galactose. Treatment of the syrup with ethanolic aniline furnished the aniline derivative of 2 : 3 : 4-tri-*O*-methyl-D-galactose, m. p. and mixed m. p. 168°. Reduction with potassium borohydride, followed by periodate oxidation, gave 0·91 mol. of formaldehyde per mol. of sugar.

Fraction 6. Chromatography of the syrup (351 mg.), $[\alpha]_D$ +108° (*c* 1·1 in H_2O), showed tri-*O*-methylgalactose (R_G 0·73) and *ca.* 10% of 2 : 3-di-*O*-methylarabinose (R_G 0·67). Demethylation gave galactose and a small amount of arabinose. Reaction with ethanolic aniline afforded the aniline derivative of 2 : 3 : 4-tri-*O*-methyl-D-galactose, m. p. and mixed m. p. 167°, and from the mother-liquors, after repeated fractional crystallisations, the aniline derivative of 2 : 4 : 6-tri-*O*-methyl-D-galactose, m. p. and mixed m. p. 178—180°. Periodate oxidation of the derived mixture of glycitols gave 0·64 mol. of formaldehyde per mol. of sugar. If 10% of 2 : 3-di-*O*-methylarabinose is assumed to be present in the fraction, the fraction contained 2 : 3 : 4- (54%) and 2 : 4 : 6-tri-*O*-methyl-D-galactose (36%).

Fraction 7. Chromatography of the syrup (53 mg.), $[\alpha]_D$ +109° (*c* 0·53 in H_2O), showed a mixture of tri-*O*-methylgalactose (R_G 0·73) and 2 : 6-di-*O*-methylgalactose (R_G 0·54).

Fraction 8. The crystalline material (1·885 g.) had $[\alpha]_D$ +112° ⟶ +85° (*c* 0·91 in H_2O), and recrystallisation from acetone containing 1% of water furnished 2 : 4-di-*O*-methyl-D-galactose monohydrate, m. p. and mixed m. p. 103° and $[\alpha]_D$ +122° ⟶ +85° (*c* 1·0 in H_2O) (Found: OMe, 27·1. Calc. for $C_8H_{16}O_6,H_2O$: OMe, 27·2%) (aniline derivative, m. p. and mixed m. p. 217—218°). Chromatography and ionophoresis of the mother-liquor from the above recrystallisation showed a mixture of 2 : 4- and 2 : 6-di-*O*-methylgalactose. The syrup (228 mg.) was separated on cellulose (50 × 2 cm.) with solvent D as eluant to give three fractions. Chromatography of fraction 8(i) (39 mg.) showed 2 : 6-di-*O*-methylgalactose (R_G 0·54) and a trace of (?) 2-*O*-methylarabinose (R_G 0·38). Demethylation gave galactose and a trace of arabinose. Chromatography of the periodate-oxidation products showed methoxymalondialdehyde (from 2 : 6-di-*O*-methylhexoses and 2-*O*-methylpentoses). The main component was characterised as 2 : 6-di-*O*-methyl-D-galactose monohydrate, m. p. and mixed m. p. 99—100° and $[\alpha]_D$ +52° ⟶ +84° (*c* 0·36 in H_2O) (Found: OMe, 27·0. Calc. for $C_8H_{16}O_6,H_2O$: OMe, 27·2%) (aniline derivative, m. p. and mixed m. p. 121—122°). Chromatography of fraction 8 (ii) (27 mg.) and its periodate-oxidation products [17] showed 2 : 4- and 2 : 6-di-*O*-methylgalactose together with a trace of the 2 : 3-dimethyl ether. Fraction 8(iii) (151 mg.), $[\alpha]_D$ +115° ⟶ +85° (*c* 1·0 in H_2O), after recrystallisation afforded 2 : 4-di-*O*-methyl-D-galactose monohydrate, m. p. and mixed m. p. 102° (aniline derivative, m. p. and mixed m. p. 216—218°).

Fraction 9. Chromatography of the syrup (108 mg.) and its periodate-oxidation products [17] showed a complex mixture of sugars, including 2 : 3-, 2 : 4-, and 2 : 6-di-*O*-methylgalactose, 2-*O*-methylarabinose, and 2-*O*-methylgalactose, which was not examined further.

Fraction 10. The chromatographically pure sugar (224 mg.), R_G 0·29 and $[\alpha]_D$ +61° ⟶ +85° (*c* 1·0 in H_2O), crystallised from glacial acetic acid and had m. p. and mixed m. p. (with 2-*O*-methyl-D-galactose) 146°.

Fraction 11. Chromatography of the syrup (42 mg.) showed galactose, arabinose, and 2-*O*-methylgalactose in approximately equal amounts.

Fraction 12. Removal of barium ions by treatment with Amberlite resin IR–120(H) followed by concentration gave a syrup (165 mg.), which was converted into the methyl ester methyl glycoside by refluxing methanolic 3% hydrogen chloride (50 ml.) during 6 hr. (constant rotation). The cooled solution was neutralised with silver carbonate, filtered and concentrated, and the product was heated with 0·15N-barium hydroxide (10 ml.) at 60° for 5 hr. After removal of barium ions with Amberlite resin IR–120(H), the acid glycoside was absorbed on Amberlite resin IR–4B(OH). Elution of the resin with N-sodium hydroxide and removal of sodium ions gave a syrup (102 mg.), which was re-esterified by refluxing it with methanolic hydrogen chloride. Lithium aluminium hydride (240 mg.) in tetrahydrofuran (10 ml.) was

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added slowly to a solution of the ester glycoside in tetrahydrofuran (30 ml.), and the mixture was refluxed for 2 hr. Excess of hydride was destroyed by water, the mixture was taken to dryness, and the residue was extracted exhaustively with chloroform and acetone to give a syrup (91 mg.). Hydrolysis of the syrup with N-hydrochloric acid at 100° for 4 hr. gave a mixture of sugars (74 mg.) which was separated on cellulose (50 × 2 cm.) with light petroleum (b. p. 100—120°)–butan-1-ol, saturated with water, to give fractions (i) (26 mg.) and (ii) (30 mg.). Fraction (i) was characterised as 2 : 3 : 4-tri-*O*-methyl-D-glucose by conversion into the aniline derivative, m. p. and mixed m. p. 133—135°. Fraction (ii), $[\alpha]_D$ +115° (*c* 0·3 in H_2O), was characterised as 2 : 3 : 4-tri-*O*-methyl-D-galactose by conversion into the aniline derivative, m. p. and mixed m. p. 169°.

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337. *Infrared Absorption Spectra of Some Urea Complexes.*

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Information about the structure of urea in a urea complex and the endocytic molecules contained therein may be obtained from infrared absorption spectra. Several complexes of aliphatic compounds, including paraffins, bromides, alcohols, acids, and esters, have been examined in this respect.

THE many investigations [1] into the crystalline complexes between urea or thiourea and various organic compounds have been used, in the main, for separation of lower and higher members of homologous series, and of branched from straight-chain compounds. Measurement of the heats of formation [2] of these " adducts " together with *X*-ray diffraction studies [3] showed that no chemical changes had occurred but that the crystal structure of the urea had been altered from a tetragonal to a hexagonal form. Further, the urea molecules were shown to be arranged in a lattice structure such that the holes in the crystals were in the form of spirals. The molecules of the reactant had taken up an endocytic position. This spiral configuration was found to be stable only in the presence of the confined molecule. The molecules inside the spiral were found to be aligned end to end.

Except for a paper by Stuart [4] on the NH stretching frequencies of the urea–cetane complex, no detailed infrared investigation of these complexes has been carried out.* As hydrogen-bond changes which play an integral part in urea-complex formation have been studied extensively by infrared measurements, it was thought that such investigations would provide information on both the changes in structure of the urea and perhaps of the molecules in the complex. So attempts were made to form urea complexes with

* After this paper had been written, our attention was drawn to work [5] on the NH stretching frequencies of urea complexes containing paraffins, alcohols, mono- and di-carboxylic acids, esters, diamines, and polymethylene halides. The results quoted show that the paraffins, alcohols, and monocarboxylic acids and esters give " normal " complexes with shifts of the asymmetric νNH vibration to longer wavelengths by 43 and 72 cm.$^{-1}$ and the symmetric νNH vibration by 125 cm.$^{-1}$ (urea, 3443 and 3347 cm.$^{-1}$). The complexes of dicarboxylic acids, diamines, and polymethylene halides, however, exhibit different absorptions in the νNH region. Thus these complexes must have a different structure from the " normal " one.

[1] McLaughlin, " The Chemistry of Petroleum Hydrocarbons," Vol. I, Chapter 10, Reinhold Publ. Corp., New York, 1954.
[2] Redlich *et al.*, *J. Amer. Chem. Soc.*, 1950, **72**, 4153, 4161.
[3] Smith, *Acta Cryst.*, 1952, **5**, 224.
[4] Stuart, *Rec. Trav. chim.*, 1956, **75**, 906.
[5] Illuminati, Grassini, and Scrocco, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1958, **24**, 435.

molecules which had been studied previously by infrared methods. Straight-chain molecules were chosen, as branched-chain and cyclic compounds usually have too large a cross-sectional area to form urea complexes.

Work on similar lines for thiourea complexes will be reported elsewhere.

Experimental.—Spectroscopic measurements were made with a Grubb-Parsons S3 spectrometer (with a sodium chloride prism), with a D.B.1 double-beam radiation unit, and with a Grubb-Parsons G.S.3 grating spectrometer.

The compounds examined were good-quality materials whose physical constants have been reported. The potassium chloride disc technique was used. The potassium chloride was heated for several days in a muffle furnace at 350—400° alternating with grinding to ensure the absence of moisture. The grinding time of the complex and potassium chloride mixture was kept as short as possible as it was thought that long grinding would break up the structure of the complex. Spectra of Nujol mulls of the complexes were essentially similar to those of the discs.

The complexes were prepared by addition of a small amount of the compound to be included to a saturated methanolic solution of urea. The crystalline adduct which formed instantaneously was filtered off under suction and washed rapidly with ether.

Besides the complexes discussed, decane formed a complex, whereas tetramethylene chloride and bromide, pentamethylene and hexamethylene glycol, valeric acid, and disodium adipate did not.

Discussion.—The spectra of urea and the urea complexes (as potassium chloride discs) are shown in Fig. 1. When compared with that of urea, all show similar changes. The adipic acid complex seems to be peculiar and will be considered below. The absorptions of urea in the free state and in the complexes are added in the Table. The shift of frequencies in the NH stretching region to longer wavelengths in the complexes suggests an increase in hydrogen bonding, this being in accordance with *X*-ray data for N–O distances: [3]

Urea	N–H···O = 3·03 Å N–H···O = 2·99 Å	Tetragonal form	
Urea–cetane complex	N^1–H···O^2 = 3·04 Å N^1–H···O^2 = 2·93 Å	Hexagonal form	

Aliphatic CH stretching vibrations occur at *ca.* 2920 and 2850 cm.$^{-1}$ and these together with shoulders at *ca.* 1465 cm.$^{-1}$, due presumably to $\delta(CH_2)$ bending vibrations, are the only positive indications that the complexes in Fig. 1 contain endocytic molecules. The changes in the absorptions due to the urea, however, indicate that complexes are formed.

This increase in bond distance in the complex gives rise to different force constants for the C=O groups and also probably different frequencies for the δNH_2 bending vibrations.

The symmetric and the asymmetric νC–N vibrations in urea [6,7] at 1457 and 1000 cm.$^{-1}$ are thought to occur at *ca.* 1485 and *ca.* 1011 cm.$^{-1}$ in the spectra of the complexes. This corresponds to a slight decrease in bond distance which has been measured by *X*-rays (C–N in urea 1·37 Å, in urea–hexadecane 1·33 Å).

The changes in frequency in the 791—717 cm.$^{-1}$ region may well result from the changes in bond angles indicated by *X*-ray evidence,[3] C–N–H···O being 116° and 136° in the complex and 99° and 128° in urea.

An alternative explanation, that the frequency changes observed on going from urea to complex may be due to different coupling between molecules in the tetragonal and hexagonal lattices, is thought not to be as good as that put forward here which correlates with *X*-ray measurements of bond distances and angles.

Other bands which occur in the spectra *C*, *D*, and *E* in Fig. 1 are due to the endocytic molecules.

In the spectra of the hexanoic acid–urea complex, the νC=O stretching vibration occurs at the same frequency as in liquid hexanoic acid.[8] Weakish absorptions at 1312, 1292,

[6] Stewart, *J. Chem. Phys.*, 1957, **26**, 248.
[7] Yamaguchi, Miyazawa, Shimanouchi, and Mizushima, *Spectrochim. Acta*, 1957, **10**, 170.
[8] Corish and Chapman, *J.*, 1957, 1746.

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1258, and 1205 (sh) cm.$^{-1}$ show more similarity to the spectrum of crystalline hexanoic acid than to that of the liquid state. These weak bands are intensified on running difference spectra of the complex *versus* urea, both as potassium chloride discs. Similarly for the pelargonic acid–urea complex (*C*), the νC=O stretching vibration corresponds to that in the

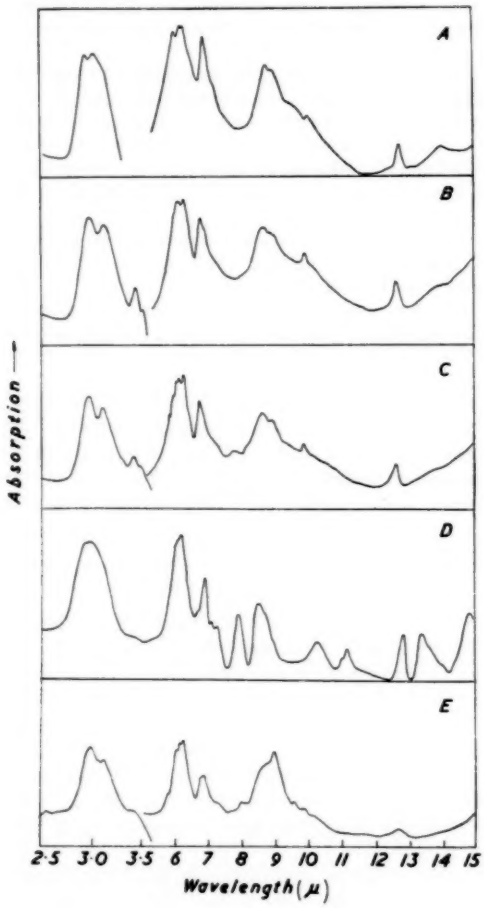

FIG. 1. *Infrared spectra of* (*A*) *urea and urea complexes with* (*B*) *cetane,* (*C*) *pelargonic acid,* (*D*) *adipic acid, and* (*E*) *diethyl adipate* (*all in* KCl *discs*).

liquid state [8] whereas weak absorptions at 1450, 1290, 1264, 1230 and ~1195(?) cm.$^{-1}$ correspond more closely to the spectrum of crystalline pelargonic acid. Difference spectra of the complex *versus* urea bring these bands up more strongly. It seems therefore that the $[CH_2]_n$ chains of the monocarboxylic acids are in a *trans*-zig-zag form but that the carboxyl groups are in similar environments to those in the liquid state.

The diethyl adipate complex (*E*) has a carbonyl absorption at a frequency corresponding to that of liquid diethyl adipate.[9] An absorption due to a $\delta(CH_3)_s$ vibration at 1382 cm.$^{-1}$ also corresponds more closely to that in liquid diethyl adipate. Weakish, but sharp, absorptions at 1266, 1053, 1018(?), and 866 cm.$^{-1}$ correspond to those in crystalline diethyl adipate. A difference spectrum of a diethyl adipate–urea complex *versus* urea (both as

[9] Corish and Davison, *J.*, 1958, 927.

Infrared frequencies (cm.$^{-1}$).

Urea	Urea in complexes *		Lit.†	Assignments
3404	3350	3400	(3420)[4]	νNH out of phase [4]
		3350	(3360) [4]	
3317	3200		(3225) [4]	νNH in phase [4]
3209(sh)			(3190) [4]	
1668			1686 [7]	Combination of CO stretch and NH_2 bend [7]; ν(CO) [6]
1620			1629 [7]	NH_2 bending,[7] δNH deformation [6]
1603			1600 [7]	Combination of CO stretch and NH_2 bend [7]; δNH deformation [6]
	4 bands 1675–1590			Probably due to different combination of CO stretch and NH bend taken in pairs
1457	1485		1464 [7]	ν(C–N) [6, 7]
1150	1160		1150 [7]	A_1NH_2 rocking,[6] A_1 and B_2NH_2 rocking [7]
(1120)				
1058	1058(w)		1050 [7]	B_2NH_2 rocking,[6] B_1NH_2 wagging [7]
1000	1011		1000 [7]	ν(C–N) [6, 7]
786	791		786 [7]	Out of plane skeletal [6] mode; NH_2 wagging + CO out of plane
717			717 [7]	B_1NH_2 wagging; [6] NH_2 wagging + CO out of plane

* These frequencies relate to complexes of urea with cetane, cetyl bromide, lauryl alcohol (which give essentially similar spectra), and to urea complexes of hexanoic acid, pelargonic acid, and diethyl adipate, but not to that of adipic acid. † Values quoted are for urea only.

potassium chloride discs) brings out these similarities more clearly. Fig. 2 shows the difference spectrum and also spectra of liquid and crystalline diethyl adipate run at the same time over the same chart. It may be deduced that the $[CH_2]_4$ part of diethyl adipate

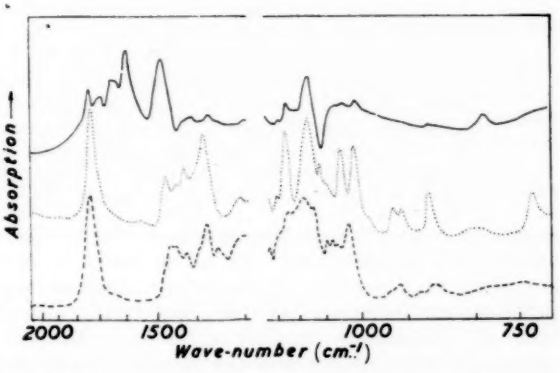

FIG. 2. *Difference spectrum of a diethyl adipate–urea complex.*

—— *Difference spectrum of complex* versus *urea* (both as KCl discs).
. . . . *Diethyl adipate (crystalline).*
– – – – *Diethyl adipate (liquid).*

is in the *trans*-zig-zag form, but the CO_2Et part is in a similar environment to that in the liquid state.

The adipic acid–urea complex (*D*) is of different structure. The complex appears to have been formed, as the bands due to the urea, *i.e.*, at 1656, 1618, 1451, and 780 cm.$^{-1}$, differ from those in urea but they also differ from those in the other complexes. In particular, the 786 cm.$^{-1}$ band due to a skeletal mode in urea has apparently moved to a longer wavelength (780 cm.$^{-1}$) and not to a shorter wavelength (791 cm.$^{-1}$) as in the urea–paraffin complexes. The absorptions due to the adipic acid, however, are somewhat different from those in the crystalline state.[10] There is a rather broad band at 747 cm.$^{-1}$, the δ(OH) out-of-plane deformation vibration at 921 cm.$^{-1}$ has moved to 975 cm.$^{-1}$ and weakened, and several additional absorptions (compared with the spectrum of crystalline adipic acid) are present. It is thought that some of the adipic acid molecules are constrained into a non-*trans*-configuration, perhaps *ttg*, where t = *trans*, g = *gauche* (cf. dimethyl and diethyl pimelate [10]). This would account for the shorter-wavelength band (747 cm.$^{-1}$) and for the

[10] Corish and Davison, *J.*, 1955, 2431.

additional absorptions at 892 and 907 cm.$^{-1}$. A shoulder at 1685 cm.$^{-1}$, however, is the same as in crystalline adipic acid, so that the C=O group is still similarly hydrogen-bonded. The 3 μ region reveals little detail, a broad OH band being centred about 3290 cm.$^{-1}$. The possibility that a reaction between urea and adipic acid causes some of these peculiarities in spectrum was eliminated, since washing with water gave a residue of pure adipic acid. The complex therefore seems to have been formed.

From the foregoing it is seen that use of the potassium chloride disc technique reveals whether a urea complex has been formed, what changes have occurred in the urea structure, and also sometimes information about the structure of the endocytic molecules. The use of differential or difference spectroscopy is valuable for this work.

This work was carried out in the Central Research Division of the Dunlop Rubber Company and we thank the Directors for permission to publish. We also thank our colleague Mr. C. G. Baker for obtaining some of the spectra.

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FORT DUNLOP, BIRMINGHAM, 24. [*Received, November 25th*, 1958.]

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338. *The Stability of Iron Complexes. Part IV.* Ferric Complexes with Aliphatic Acids.*

By D. D. PERRIN.

In acid solutions, ferric ion and aliphatic acids form complexes of the types $Fe(CH_3{\cdot}CO_2)^{2+}$ and $Fe_3(OH)_2(CH_2{\cdot}CO_2)_6^{+}$. The stability constants of the complexes for the series chloroacetic, formic, acetic, propionic, and *iso*butyric acids have been obtained at 20° and $I = 1$, in a medium consisting essentially of sodium perchlorate, from oxidation–reduction potentials. The stability of the complexes increases in the order given above for the acids. Several of the 3 : 2 : 6 complexes have high stability constants, of the order of 10^{20}. Stability constants have also been calculated for the corresponding 1 : 1 ferrous complexes with chloroacetic, acetic, and propionic acids.

STABILITY constants have been tabulated [1] for complexes of aliphatic acids with several cations, but not with iron. The amber colour of ferric acetate solutions suggests that complexes are present, and ferric acetates which are believed to be salts of the complexes, penta-acetatodihydroxytriferri-base and hexa-acetatodihydroxytriferri-base, have been isolated.[2] Evidence in support of the latter has also been obtained by electrometric titration of ferric chloride with sodium acetate [3] and by dialysis-coefficient measurements.[4] Similar complexes have been prepared with chloroacetic,[5] formic,[6] and propionic acids.[7] Electrometric titration confirms that these, and the corresponding butyric acid complex, are present in aqueous solution.[8] A ferric-hexaformate ion, $Fe(H{\cdot}CO_2)_6^{3-}$, has also been reported.[6] Ferric triacetate, which has with difficulty been crystallised from acetic acid,[9] is believed to be trimeric.[10] In all these cases, observations have been made only at high

* Part III, *J.*, 1959, 290.

[1] Bjerrum, Schwarzenbach, and Sillén, "Stability Constants. Part I: Organic Ligands," The Chemical Society, London, Spec. Publ. No. 6, 1957.
[2] Weinland, Kessler, and Bayerl, *Z. anorg. Chem.*, 1924, **132**, 209.
[3] Treadwell and Fisch, *Helv. Chim. Acta*, 1930, **13**, 1209.
[4] Brintzinger and Jahn, *Z. anorg. Chem.*, 1936, **230**, 176.
[5] Weinland and Loebich, *ibid.*, 1926, **151**, 277.
[6] Weinland and Reihlen, *Ber.*, 1913, **46**, 3144.
[7] Weinland and Höhn, *Z. anorg. Chem.*, 1926, **152**, 1.
[8] Treadwell and Fisch, *Helv. Chim. Acta*, 1930, **13**, 1219.
[9] Krause, *Z. anorg. Chem.*, 1928, **169**, 273.
[10] Gmelin's "Handbuch der anorganischen Chemie," Verlag Chemie, Berlin, 1932, 8th edn., System number 59, B, p. 526.

concentrations. No intermediate complexes have been reported, although it has been suggested [8] that complex formation might proceed through the ion $FeOH^{2+}$. As would be expected,[11] ferric ion forms more stable complexes with aliphatic acid anions than does ferrous ion.[3,8]

In the present work, oxidation–reduction potentials have been used to obtain quantitative information on the kinds, and stabilities, of complexes formed by ferric ion in less concentrated aliphatic acid solutions. To ensure that conditions were chosen so that ferrous complex formation was negligible, preliminary estimates were obtained of log K_1 ($\sim 0{\cdot}6$) and log β_2 ($\sim 1{\cdot}2$) for ferrous–acetate complexes, using results for nickel–acetates [12] and assuming Irving and Williams's relation.[13] A value of log $K_1 = 0{\cdot}3$ was subsequently found by experiment. Ferrous complex formation should therefore have been negligible ($<5\%$) for acetate-ion concentrations less than 0·024M. The same concentration limit was assumed for the other acids.

Experimental

Ferric and ferrous perchlorates were prepared as already described.[11] All oxidation–reduction potential and pH measurements were made at 20° in sodium perchlorate–perchloric acid solutions of approximately unit ionic strength, as described previously.[11] The dissociation constants (pK) of chloroacetic, formic, acetic, propionic, and *iso*butyric acids in 1M-sodium perchlorate were found by potentiometric titration to be $2{\cdot}60 \pm 0{\cdot}01$, $3{\cdot}49 \pm 0{\cdot}02$, $4{\cdot}55 \pm 0{\cdot}01$, $4{\cdot}66 \pm 0{\cdot}01$, and $4{\cdot}63 \pm 0{\cdot}01$, respectively. These constants were calculated from the concentrations of the free acid and its anion, and the hydrogen-ion activity as measured by the glass electrode.

Hydrolysis of Ferric Ion.—Because correction for hydrolysis of ferric ion was more important than in earlier Parts of this series, the acid dissociation constants, $^*K_1$, $^*\beta_2$, and $^*\beta_{22}$, of ferric ion, corresponding to the formation of $FeOH^{2+}$, $Fe(OH)_2^{+}$, and $Fe_2(OH)_2^{4+}$, were determined under the present experimental conditions. (Symbols used in this paper are the same as in Bjerrum, Schwarzenbach, and Sillén, "Stability Constants. Part II: Inorganic Ligands," The Chemical Society, London, Spec. Publ. No. 7, 1958). If a constant total ferric–ferrous concentration ratio is maintained and complex-forming species are absent, the pH-dependence of the ferric–ferrous potential, E, enables $^*K_1$, $^*\beta_2$, and $^*\beta_{22}$ to be obtained.[11,14] Thus, if the approximations are made that at constant ionic strength the liquid-junction potential and the activity coefficients of ferric and ferrous ion do not change appreciably as the pH of the solution is varied:

$$\text{antilog}\{(E_0' - E)/0{\cdot}0581\} = [Fe^{3+}]_T/[Fe^{3+}] = 1 + {}^*K_1/[H^+] + {}^*\beta_2/[H^+]^2 + 2{}^*\beta_{22}[Fe^{3+}]/[H^+]^2 \quad . \quad . \quad . \quad . \quad \text{(i)}$$

where E_0' is the potential of the experimental ferric–ferrous ratio under conditions where no hydrolysis occurs, and $[Fe^{3+}]_T$ is the total concentration of ferric iron. E_0' must be obtained by extrapolation because, at the high concentrations of hydrogen ion that are necessary before hydrolysis of ferric ion becomes negligible, the liquid-junction potential can no longer be assumed constant. If a ferric–perchlorate complex ion, $FeClO_4^{2+}$, was also present in the solution,[15] the form of eqn. (i) would remain unchanged but each stability constant would include the term, $1/(1 + K[ClO_4^-])$, where K is the stability constant of $FeClO_4^{2+}$. In 1M-sodium perchlorate solutions, and low ferric-ion concentrations, E reached a maximum near pH 1·7; E_0', obtained by successive approximation using eqn. (i), was 1·5 mv greater than this.

The results shown in Fig. 1 were obtained from titrations of acid solutions of ferric and ferrous perchlorates with sodium hydrogen carbonate and of less acid solutions with perchloric acid. From them, $^*K_1 = 1{\cdot}8 \times 10^{-3}$, $^*\beta_2 = 8{\cdot}9 \times 10^{-7}$, at 20°, in 1M-sodium perchlorate solution. Similarly, from the results in Table 1 for higher concentrations of ferric ion, $^*\beta_{22} = 1{\cdot}4 \times 10^{-3}$. From spectrophotometric measurements under these conditions, but without

[11] Perrin, *J.*, 1958, 3120.
[12] Fronaeus, *Acta Chem. Scand.*, 1952, **6**, 1200.
[13] Irving and Williams, *J.*, 1953, 3192.
[14] Hedström, *Arkiv Kemi*, 1953, **6**, 1.
[15] Horne, *Nature*, 1958, **181**, 410.

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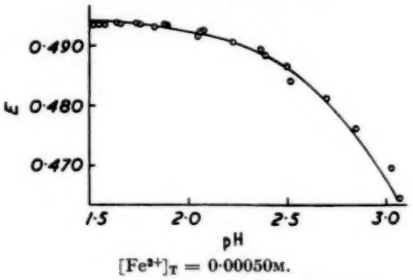
correction for the presence of the 1 : 2 complex, Milburn [16] obtained ${}^*K_1 = 1{\cdot}22 \times 10^{-3}$, ${}^*\beta_{22} = 1{\cdot}5 \times 10^{-3}$. Estimates, by interpolation from earlier results, were [17] ${}^*K_1 = 7 \times 10^{-4}$, ${}^*\beta_2 = 4 \times 10^{-7}$, and ${}^*\beta_{22} = 1 \times 10^{-3}$. In the present work, formation of $Fe_2(OH)_2^{4+}$ was significant only at the highest ferric-ion concentrations.

Ferric–Acetate Complexes.—Although stable and reproducible oxidation–reduction potentials were obtained in perchlorate solutions containing ferric ion, ferrous ion, and acetic acid, preliminary experiments showed that these potentials depended on several independent

FIG. 1. *Hydrolysis of* Fe^{3+}.



$[Fe^{3+}]_T = 0{\cdot}00050$M.

Curve is for $E = 0{\cdot}4956 - 0{\cdot}0581 \log\left(1 + \frac{1{\cdot}08 \times 10^{-3}}{[H^+]} + \frac{8{\cdot}9 \times 10^{-7})}{[H^+]^2}\right)$

variables: (i) At constant pH and constant free ferric-ion concentration, potentials varied with acetate-ion concentration. (ii) At constant free ferric-ion and acetate-ion concentrations, potentials were pH-dependent. (iii) At constant pH, acetate-ion concentration and ferric–ferrous ratio, potentials varied with ferric-ion concentration. On the other hand, the presence

TABLE 1. *Evaluation of* ${}^*\beta_{22}$ *from oxidation–reduction potentials.*

$[Fe^{3+}]_T = 0{\cdot}050$M. 1M in $NaClO_4 + HClO_4$. ${}^*K_1$ and ${}^*\beta_2$ obtained from Fig. 1.

pH	$E_0 - E$	$[Fe^{3+}]_T/[Fe^{3+}]$	${}^*K_1/[H^+] + {}^*\beta_2/[H^+]^2$	$-\log {}^*\beta_{22}$
1·89	0·0108	1·535	0·089	2·92
2·04	0·0163	1·907	0·130	2·88
2·22	0·0242	2·611	0·204	2·84
2·32	0·0287	3·118	0·265	2·84
2·41	0·0332	3·730	0·332	2·84

or absence of acetic acid did not appear to affect the ferric–ferrous potential observed in high concentrations of perchloric acid.

These results were interpreted to mean that complex formation occurred between ferric and acetate ions, that some or all of the complexes formed were ferric hydroxy-acetates, and that polynuclear complexes were present.

To obtain an estimate of the average number of ferric ions in the complexes, potential measurements were made at constant pH and constant acetate- and ferrous-ion concentrations but with varying amounts of ferric ion. Now if β_{xyz} ($x \geqslant 1$; $y, z \geqslant 0$) is the overall stability constant of any complex, $Fe_x(OH)_yL_z$, it can be deduced (see Appendix) from the electrode equation and the mass-action equation, that

$$\frac{0{\cdot}0581}{\partial E/\partial \log [Fe^{3+}]_T} = \frac{\sum x^2\beta_{xyz}[Fe^{3+}]^x[H^+]^{-y}[L^-]^z}{\sum x\beta_{xyz}[Fe^{3+}]^x[H^+]^{-y}[L^-]^z} \quad \ldots\ldots \text{(ii)}$$

where $[Fe^{3+}]_T$ is the total concentration of tervalent iron and $[Fe^{3+}]$ is the concentration of free ferric ion, provided only that the activity coefficients of the various ionic species remain constant. Eqn. (ii) is independent of the extent of any ferrous complex formation. Hence the slope of the plot of $0{\cdot}0581 \log [Fe^{3+}]_T$ against E depends on the degree of aggregation of the complexes; for any ferric-ion concentration the slope gives directly the average number of ferric ions that occur together in the solution.

[16] Milburn, *J. Amer. Chem. Soc.*, 1957, **79**, 537.
[17] Perrin, *J.*, 1958, 3125.

Results plotted in Fig. 2, for a solution 0·058M in acetate ion and of pH 2·77, give a slope close to 3·0 as ferric iron varies from 5×10^{-5} to 1×10^{-2}M. In a similar experiment, at pH 2·37 and an acetate concentration of 0·0037M, the slope was about 2 for ferric-ion concentrations between 5×10^{-5} and 5×10^{-4}M, increasing to near 3 at higher concentrations.

The compositions and stability constants of the main complexes present were then sought. From the observed oxidation–reduction potentials, the ratio $[Fe^{3+}]_T/[Fe^{3+}]$, and hence $[Fe^{3+}]$, was calculated by using eqn. (i). But, in the presence of complex-forming species: [11]

$$[Fe^{3+}]_T/[Fe^{3+}] - (1 + \delta) = \sum x\beta_{xyz}[Fe^{3+}]^{x-1}[H^+]^{-y}[L^-]^z \quad (= R) \quad . \quad . \quad . \quad \text{(iii)}$$

where δ, the correction term for hydrolysis of ferric ion, is ${}^*k_1/[H^+] + {}^*\beta_2/[H^+]^2 + 2{}^*\beta_{22}[Fe^{3+}]/[H^+]^2$, and x,y,z have the same significance as in eqn. (ii). When mainly one complex is present, eqn. (iii) can be written:

$$\log R - (x - 1) \log [Fe^{3+}] \simeq z \log [L^-] + y \text{ pH} + \log \beta_{xyz} + \log x \quad . \quad . \quad \text{(iv)}$$

The data in Fig. 3 were obtained where ferric iron was present mainly in trimeric complexes: this conclusion was based on the results discussed above. It was assumed, and subsequently

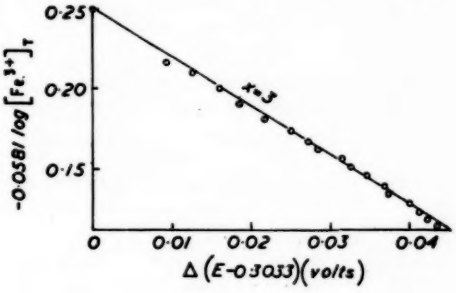


FIG. 2. *Determination of degree of aggregation of ferric iron in acetate solutions.*
pH = 2·77. $[OAc^-]$ = 0·058M.

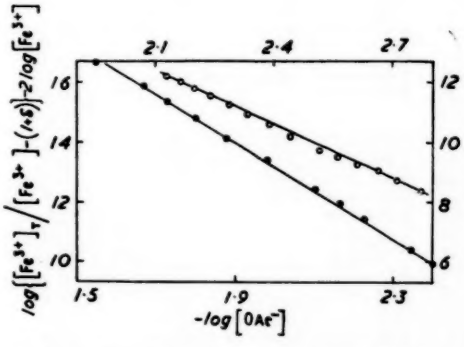


FIG. 3. *Determination of number of acetate and hydroxyl radicals in ferric complex.*
○ $[Fe^{3+}]_T$ = 0·00463M; pH = 2·40.
● $[Fe^{3+}]_T$ = 0·00425M; pH range 1·90—2·79.
Scales top and right are for open circles.

confirmed from the stability constants obtained in the present work, that only one complex was important over the two ranges studied in Fig. 3. In the first experiment, made at constant pH (2·40), the plot of log R − 2 log $[Fe^{3+}]$ against log $[L^-]$ gave $z = 6$. In the second experiment, at constant acetic acid concentration, but at varying pH, plotting the same quantities should give a line of slope, $y + z$. (This follows from the identity, pH = pK + log $[L^-]$ − log [HL]). In this way, a value of $y + z = 8$ was obtained. That is, the complex is $Fe_3(OH)_2(OAc)_6^+$. From the two sets of data in Fig. 3, the overall log stability constant, log β_{226}, for $[Fe_3(OH)_2(OAc)_6^+][H^+]^2/[Fe^{3+}]^3[OAc^-]^6$, is 19·6 and 20·0, respectively. The value of this constant is extremely dependent on the accuracy of the pH measurement (which determines both $[OAc^-]$ and $[H^+]$).

The results summarised in Tables 2 and 3 were obtained from measurements on solutions the compositions of which were varied by small, successive additions of 1M-$NaHCO_3$, 1M-$HClO_4$, or acetic acid–sodium acetate mixtures. As shown in Table 2, the assumption that only the

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3 : 2 : 6 complex is present gives consistent stability constant values over wide range of conditions, with a mean value of log $\beta = 19{\cdot}8$.

TABLE 2. *The stability constant of* $Fe_3(OH)_2(OAc)_6^+$ *at 20° and unit ionic strength.*

$[Fe^{3+}]_T$(M)	pH	log R*	−log $[Fe^{3+}]$	− log $[L^-]$	log $\beta \pm$ S.E. (no. of obs.)
0·000050	2·28—2·79	0·83—2·12	5·23—6·50	1·75—2·38	19·9 ± 0·2 (9)
0·000050	3·18—3·19	1·30—2·88	5·70—7·23	1·53—2·39	19·8 ± 0·2 (16)
0·00050	2·50	0·33—2·00	3·86—5·36	2·06—2·89	19·6 ± 0·1 (17)
0·0050	1·93—2·18	0·94—1·64	3·33—4·02	2·44—2·93	20·1 ± 0·1 (8)
0·0050	2·19—3·01	0·26—3·90	2·83—6·30	1·66—3·18	19·9 ± 0·2 (15)
0·050	2·33—2·41	1·73—1·94	3·11—3·33	2·78—2·98	20·3 ± 0·1 (9)
0·050	2·33—2·99	1·94—4·45	3·33—5·87	1·68—2·78	19·9 ± 0·1 (21)
				Overall mean	19·8 ± 0·2 (95)

* $R = [Fe^{3+}]_T/[Fe^{3+}] - (1 + \delta)$.

TABLE 3. *The stability constant of* $FeOAc^{2+}$ *at 20° and unit ionic strength.*

$[Fe^{3+}]_T$(M)	pH	$R_{corr.}$*	− log $[Fe^{3+}]$	− log $[L^-]$	log $K_1 \pm$ S.E. (no. of obs.)
0·000050	2·50	0·24—3·27	4·57—5·13	2·48—3·58	3·0 ± 0·05 (8)
0·000050	1·73—2·28	1·10—9·75	4·71—5·42	2·27—2·82	3·1 ± 0·2 (3)
0·000050	3·19—3·24	1·71—11·7	5·13—5·61	2·49—3·34	3·5 ± 0·03 (5)
0·00050	2·50	0·33—0·84	3·55—3·72	3·06—3·58	3·1 ± 0·02 (4)
0·0050	1·86—2·12	0·12—2·99	2·43—3·07	3·05—4·16	3·3 ± 0·1 (8)
0·0050	2·50	0·58—1·80	2·71—3·15	3·09—3·77	3·5 ± 0·03 (5)
				Overall mean	3·2 ± 0·2 (33)

* $R_{corr.} = [Fe^{3+}]_T/[Fe^{3+}] - (1 + \delta)$, corrected for the 3 : 2 : 6 complex, using log $\beta = 19{\cdot}8$.

TABLE 4. *Stability constants of ferric complexes of other aliphatic acids at 20° and unit ionic strength.*

$[Fe^{3+}]_T$,M	pH	log R*	− log $[Fe^{3+}]$	− log $[L^-]$	log $K_1 \pm$ S.E. (no. of obs.)	log β_{326}† ± S.E. (no. of obs.)
Chloroacetic acid						
0·0050	2·47	−0·57—+0·22	2·64—2·87	1·99—2·68	2·16 ± 0·03 (6)	
0·0050	1·05—1·25	0·77—1·11	3·07—3·41	1·07—1·26	2·10 ± 0·06 (3)	
0·0050	2·47—3·04	0·44—1·48	2·96—3·86	1·47—1·85		11·2 ± 0·2 (8)
Formic acid						
0·010	2·33—2·47	−0·11—+0·97	2·49—3·10	2·18—3·31	3·12 ± 0·04 (11)	
0·010	2·33—2·85	1·05—2·19	3·18—4·28	1·67—2·11		14·3 ± 0·2 (4)
Propionic acid						
0·00050	2·49—2·56	−0·85—+0·07	3·56—3·80	3·39—4·22	3·38 ± 0·07 (5)	
0·00050	2·48	−1·42—−0·02	3·47—3·73	3·26—4·52	3·14 ± 0·06 (8)	
0·00050	3·07—3·08	−0·63—+0·75	3·89—4·29	3·20—4·34	3·80 ± 0·11 (6)	
0·0050	2·11—2·32	−0·09—+0·39	2·61—2·88	3·27—3·76	3·63 ± 0·03 (4)	
0·00050	2·61—2·71	0·63—1·40	4·15—4·85	2·69—3·06		21·2 ± 0·03 (6)
0·00050	2·50—3·52	0·63—3·15	4·17—6·59	1·92—2·90		20·4 ± 0·2 (7)
0·00050	2·30—2·80	1·61—2·91	4·94—6·23	1·89—2·38		20·6 ± 0·1 (5)
0·00050	3·08—3·20	0·94—2·54	4·42—5·97	2·21—3·05		21·0 ± 0·1 (13)
0·0050	2·00—3·17	0·71—4·48	3·03—6·85	1·50—3·07		20·6 ± 0·1 (18)
*iso*Butyric acid						
0·00050	3·01	−0·60—+0·14	3·85—3·97	3·67—4·36	3·78 ± 0·02 (3)	
0·00050	2·50—2·52	−1·14—−0·51	3·52—3·59	3·85—4·56	3·35 ± 0·18 (3)	
0·00050	2·97—3·06	0·33—2·28	4·04—5·68	2·57—3·50		22·3 ± 0·2 (10)
0·00050	2·56—2·63	0·47—1·43	4·01—4·85	2·80—3·23		21·9 ± 0·1 (6)

* $R = [Fe^{3+}]_T/[Fe^{3+}] - (1 + \delta)$.
† Corrected for 1 : 1 complex, using appropriate mean log K_1.

Summary of Table 4.

Acid	pK	log K_1	log β_{326}	Acid	pK	log K_1	log β_{326}
Chloroacetic	2·60	2·1 ± 0·05	11·2 ± 0·2	Propionic ...	4·66	3·45 ± 0·3	20·7 ± 0·3
Formic	3·49	3·1 ± 0·04	14·3 ± 0·2	*iso*Butyric ...	4·63	3·6 ± 0·2	22·1 ± 0·2
Acetic	4·55	3·2 ± 0·2	19·8 ± 0·2				

However, this constant underestimates the extent of complex formation at low concentrations and, to fit the results given in Table 3, it is necessary to assume that a 1 : 1 ferric–acetate complex, $FeOAc^{2+}$, is also present, with a log stability constant of 3·2. This estimate

is subject to rather large experimental uncertainty, because it is obtained under conditions where correction for hydrolysis of ferric ion becomes important and where differences in oxidation–reduction potentials are small.

Ferric Complexes with Other Aliphatic Acids.—Measurements of ferric–ferrous potentials were also made with solutions containing chloroacetic, formic, propionic, and *iso*butyric acids. At low iron concentrations in formic acid solutions, potentials were not stable but decreased steadily with time, probably indicating reduction of ferric ion; this drift was much slower at

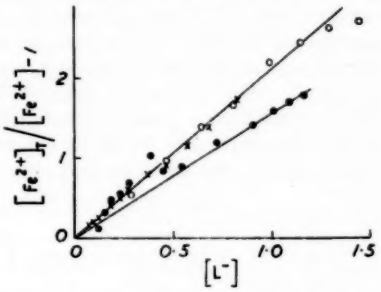


FIG. 4. *Determination of* K_1 *for 1 : 1 ferrous–aliphatic acid complexes.*
○ Acetic acid.
● Chloroacetic acid.
× Propionic acid.

high ferric concentrations. For all the acids examined, the results (Table 4) can be interpreted quantitatively on the assumption that only 1 : 1 and 3 : 2 : 6 ferric complexes are present in significant amounts.

TABLE 5. *Ferrous complex formation.*

$[Fe^{2+}]_T = [Fe^{3+}]_T = 0{\cdot}0050$M.

pH	$(E_0 - E)$/0·0581	$-\log[L^-]$	$[Fe^{2+}]_T/[Fe^{2+}]$	pH	$(E_0 - E)$/0·0581	$-\log[L^-]$	$[Fe^{2+}]_T/[Fe^{2+}]$
Chloroacetic acid							
1·40	1·373	0·932	1·12	2·21	3·009	0·263	1·88
1·52	1·600	0·821	1·33	2·41	3·322	0·140	2·19
1·62	1·798	0·731	1·49	2·60	3·597	0·042	2·41
1·72	2·016	0·644	1·56	2·71	3·733	−0·005	2·58
1·82	2·215	0·559	1·69	2·80	3·838	−0·038	2·69
2·00	2·546	0·413	2·03	2·89	3·941	−0·067	2·77
2·09	2·780	0·347	1·83				
Acetic acid							
3·73	6·397	0·540	1·54	4·52	7·66	0·003	3·19
3·99	6·875	0·332	1·96	4·67	7·85	−0·061	3·44
4·19	7·20	0·190	2·39	4·82	8·03	−0·113	3·61
4·35	7·45	0·093	2·66	5·00	8·23	−0·161	3·70
Propionic acid							
2·85	4·540	1·519	1·06	3·87	6·935	0·568	1·61
3·10	5·166	1·275	1·13	4·04	7·272	0·430	1·80
3·25	5·547	1·130	1·16	4·17	7·526	0·332	1·91
3·37	5·837	1·017	1·20	4·30	7·741	0·241	2·15
3·49	6·121	0·905	1·25	4·42	7·924	0·166	2·39
3·67	6·516	0·741	1·41	4·57	8·135	0·081	2·71
3·78	6·756	0·644	1·50				

Ferrous Complexes with Aliphatic Acids.—If higher ferric complexes are not formed when the concentrations of aliphatic acid anions are increased further, evidence of ferrous complex formation can be sought from oxidation–reduction potentials, by use of the equations:

$$\log[Fe^{2+}] = (E_0 - E)/0{\cdot}0581 + 1/3 \log[Fe^{3+}]_T - 2 \log[L^-] - 2/3\ pH - 1/3 \log 3\beta_{326}$$

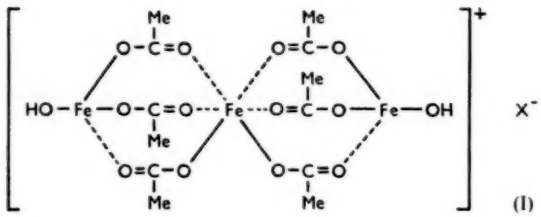
(which can be deduced from the mass action and electrode equations), and [11]

$$[Fe^{2+}]_T/[Fe^{2+}] - 1 = K_1[L^-] + \beta_2[L^-]^2 + \ldots.$$

Experimental data for chloroacetic, acetic, and propionic acids, summarised in Table 5, give $K_1 = 1{\cdot}6$, 2·1, and 2·1, respectively (Fig. 4), but are not sufficiently extensive for K_2 to be estimated.

Discussion

The present results suggest that, in acid solutions, anions of aliphatic acids form two series of stable ferric complexes. At low reactant concentrations the 1 : 1 complex, FeL^{2+}, is present. At higher concentrations the complex, $Fe_3(OH)_2L_6^+$, is the major species. The assumption that ferric-complex formation does not continue significantly beyond the 3 : 2 : 6 complex, at least in moderate concentrations of aliphatic acid anion, enables the stability constants of the 1 : 1 ferrous complexes to be obtained. This appears to be a reasonable assumption because the values so calculated are consistent with results for other cations.[1] Formic acid is anomalous; in high concentrations of formate ion a colourless complex is produced. For the acids examined, values of log β_{326} largely confirm earlier conclusions [3,8] concerning the sequence of stabilities of the ferric complexes. The increase from chloroacetate to propionate would be expected from the p*K*s of the acids, but the further increase to *iso*butyrate indicates that other factors are also involved.



(I)

The absence of appreciable concentrations of intermediate complexes implies that the 3 : 2 : 6 ferric complexes have a particularly stable configuration in solution. These complexes are probably analogous to the hexa-acetatodihydroxytrichromic complexes, first isolated by Weinland [18] and Werner.[19] In both cases it has been suggested [20] that the middle metal atom is at the centre of an octahedron, with 6 acetate radicals occupying the corners. Each of two opposite faces of the octahedron is the base of a tetrahedron, with a metal atom at its centre and a hydroxyl group at its apex. Thus the 3 : 2 : 6 ferric-hydroxyacetate complex would be as shown in (I). The alternative hypothesis, that a ring complex is formed,[21] is less convincing.[3]

The absorption spectra of the 3 : 2 : 6 ferric complexes of the aliphatic acids are very similar, with maxima at 337·5 and 465 mμ, inflexions near 395 and 515 mμ, and a minimum near 443 mμ. In addition there is a weak maximum near 448 mμ, with $\varepsilon_{448} < \varepsilon_{465}$ for the acetate complex, $\varepsilon_{448} \sim \varepsilon_{465}$ for propionate and chloroacetate, and $\varepsilon_{448} > \varepsilon_{465}$ for *iso*butyrate. Molecular extinction coefficients of 5010 and 199 were found at 337·5 and 465 mμ respectively for the ferric–acetate complex in 2M-sodium acetate–2M-acetic acid solution. In neutral and alkaline solution, changes in absorption spectra indicate that further complex formation occurs, but this has not been investigated. Except for a uniform reduction in intensity because of less complete formation of the complex, the ferric–acetate spectrum in 50% acetic acid [22] is the same as in less acid solutions. The absorption maximum at 337·5 mμ is probably similar in origin to the maximum at 335 mμ (log $\varepsilon = 4{\cdot}9$),[23] given by the dinuclear complex, $Fe_2(OH)_2^{4+}$, but not by mononuclear species such as Fe^{3+}, $FeOH^{2+}$, and $Fe(OH)_2^+$.[23]

[18] Weinland, *Ber.*, 1908, **41**, 3236.
[19] Werner, *ibid.*, p. 3447.
[20] Reihlen, *Z. anorg. Chem.*, 1920, **114**, 65.
[21] Henrichsen, in Weinland's "Einführung in die Chemie der Komplexverbindungen," F. Enke, Stuttgart, 1924, 2nd edn., p. 398.
[22] Reiss, Hazel, and McNabb, *Analyt. Chem.*, 1952, **24**, 1646.
[23] Mulay and Selwood, *J. Amer. Chem. Soc.*, 1955, **77**, 2693.

Appendix

Derivation of Equation (ii).—If

$$\beta_{xyz} = [Fe_x(OH)_yL_z][H^+]^y/[Fe^{3+}]^x[L^-]^z$$

for any complex, $Fe_x(OH)_yL_z$(where $x \geqslant 1$; $y, z \geqslant 0$), including hydrated ferric ion and its hydroxy-complexes, the total ferric-iron concentration,

$$\begin{aligned}[Fe^{3+}]_T &= \sum x[Fe_x(OH)_yL_z] \\ &= \sum x\beta_{xyz}[Fe^{3+}]^x[H^+]^{-y}[L^-]^z\end{aligned}$$

$$\text{Therefore, } \frac{\partial \log [Fe^{3+}]_T}{\partial \log [Fe^{3+}]} = \frac{[Fe^{3+}]}{[Fe^{3+}]_T} \cdot \frac{\partial [Fe^{3+}]_T}{\partial [Fe^{3+}]}$$

$$= \frac{\sum x^2\beta_{xyz}[Fe^{3+}]^x[H^+]^{-y}[L^-]^z}{\sum x\beta_{xyz}[Fe^{3+}]^x[H^+]^{-y}[L^-]^z} \quad \ldots\ldots\ (1)$$

(= x when all complexes present contain x atoms of ferric iron). But, at 20° and constant ionic strength,

$$E = E_0 + 0{\cdot}0581 \log [Fe^{3+}]/[Fe^{2+}]$$

Hence, at constant pH, $[Fe^{2+}]$, and ligand concentration,

$$\partial E/\partial \log [Fe^{3+}]_T = 0{\cdot}0581 \times \partial \log [Fe^{3+}]/\partial \log [Fe^{3+}]_T$$

i.e.,

$$\frac{0{\cdot}0581}{\partial E/\partial \log [Fe^{3+}]_T} = \frac{\partial [\log Fe^{3+}]_T}{\partial [\log Fe^{3+}]} = (1) \text{ (above)}$$

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339. *Chemical Constitution and the Dissociation Constants of Monocarboxylic Acids. Part XIX.* Dihydroxy- and Dichloro-benzoic Acids.*

By J. F. J. Dippy, S. R. C. Hughes, and L. G. Bray.

The strengths of all six dihydroxybenzoic acids and three dichlorobenzoic acids in water have been determined conductometrically. The qualitative effect of introducing a second substituent into the monosubstituted benzoic acid is consistent with expectation although in certain cases substantial departures from additivity have been observed.

The strengths of all six dihydroxybenzoic acids in water (Table 1) have now been determined by a standard procedure, and the effect of introducing a second hydroxyl group into the monohydroxybenzoic acid system is qualitatively that to be expected from a knowledge of the polar character ($-I+M$) of the hydroxyl substituent (10^5K for *o*-, *m*-, and *p*-hydroxybenzoic acids = 101, 3·27, and 2·94, respectively). Thus in both the salicylic acid and the *m*-hydroxybenzoic acid system, the introduction of a *meta*-hydroxyl group has the effect of strengthening the acid, whereas the entry of *para*-hydroxyl depresses the strength. Quantitative examination of the K data reveals, however, that only in the

* Part XVIII, *J.*, 1959, 1441.

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case of 2,4-dihydroxybenzoic acid is there absolute additivity.[1-3] This is doubtless connected with the fact that there is no possibility of steric or mesomeric interaction here between the two hydroxyl groups, whereas both of these additional factors might operate in 2,3- or 3,4-dihydroxybenzoic acids so as to modify their strengths. It is significant, therefore, that departures of −2·9% and −38% from additivity are observed with these

TABLE 1. *Dissociation constants* (10^3K).

Benzoic acid	This paper	Earlier values	M. p.	Benzoic acid	This paper	Earlier values	M. p.
2,3-Dihydroxy-	1·22	1·14 [a]	206—207°	2,6-Dihydroxy-	89	50 [a]	172° (decomp.)
2,4-Dihydroxy-	0·473	0·496 [b]	226 (decomp.)	3,4-Dihydroxy-	0·0323	0·033 [a]	203
		0·515 [a, c]		3,5-Dihydroxy-	0·0915	0·091 [a]	237—238
2,5-Dihydroxy-	1·12	1·08 [a]	201—202	2,4-Dichloro- ...	2·09		160—161
		1·10 [b]		2,5-Dichloro- ...	3·42		154
		1·18 [d]		2,6-Dichloro- ...	25·5		144
		1·30 [e]					

[a] Ostwald, *Z. phys. Chem.*, 1889, **3**, 248.
[b] Suss, *Monatsh.*, 1905, **26**, 1331.
[c] Kendall, *Chem. Zentr.*, 1914, **1**, 842.
[d] Boeschen, *Rec. Trav. chim.*, 1921, **40**, 576.
[e] Wightman and Jones, *J. Amer. Chem. Soc.*, 1924, **46**, 94.

acids; the observed departure for the 2,5-acid (where the additional mesomeric factor alone operates) is −5·5%. The remarkably high strength of 2,6-dihydroxybenzoic acid, already well-known, has received confirmation; an explanation of this feature has already been advanced.[4]

A wholly unexpected result is the strength of 3,5-dihydroxybenzoic acid which is very little greater than that of *m*-hydroxybenzoic acid and shows a departure of −32% from additivity. It is not possible to envisage any mutual interaction between the two hydroxyl groups in this structure, and the phenomenon cannot yet be explained.

The dissociation constants of three dichlorobenzoic acids have also been determined. The introduction of a second chlorine substituent into *o*-chlorobenzoic acid leads, as expected, to a substantial enhancement of strength, by virtue of the $-I$ effect, although the effect from the *para*-position (where $+M$ operates) is less than from the *meta*-position as the data in Table 1 reveal (cf. 10^3K for *o*-, *m*-, and *p*-chlorobenzoic acids = 1·14, 0·148, and 0·105, respectively). In 2,6-dichlorobenzoic acid the very large increment in strength is doubtless due to the additional steric factor introduced by the second substituent. Quantitative consideration of the data shows that entry of the second chlorine substituent produces a small departure (*ca.* +3 to +6%) from additivity in each of the three acids.

Specimens of the remaining acids of this series proved so sparingly soluble in water that even very approximate measurements of their dissociation could not be made.

These data, coupled with those published recently by us,[2,3] go some way to making good the deficiency of reliable dissociation-constant data for disubstituted aromatic acids.

EXPERIMENTAL

Materials.—2,6-Dichlorobenzoic acid was prepared from 2,6-dichlorotoluene by side-chain bromination, followed by oxidation with alkaline potassium permanganate as described by Norris and Bearse.[5] The remaining acids were purchased.

All acids were recrystallised from conductivity water or from aqueous acetone, except 2,5-dihydroxybenzoic acid which was recrystallised from benzene–acetone. Final specimens were dried in individual vacuum desiccators over silica gel for at least 3 weeks, and the equivalents were confirmed by alkalimetry.

[1] Shorter and Stubbs, *J.*, 1949, 1180.
[2] Dippy, Hughes, and Laxton, *J.*, 1956, 2995.
[3] Bray, Dippy, Hughes, and Laxton, *J.*, 1957, 2405.
[4] Baker, *Nature*, 1936, **137**, 236.
[5] Norris and Bearse, *J. Amer. Chem. Soc.*, 1940, **62**, 956.

Conductivity Measurements.—The procedure and equipment used have already been described,[6] and the values of K were derived by the usual method. Λ_0 was the self-consistent value obtained by Ives's extrapolation method,[7,8] and no additional significance is attached to such data for the present. Their use in structural considerations can be envisaged only after comparison with directly determined mobilities. The specific conductance of the water employed was 0·5—0·8 gemmho. Results are detailed in Table 2 (concentrations in moles $l.^{-1}$; Λ in mhos $cm.^2$).

TABLE 2.

10^2C	Λ	10^3K
2,3-Dihydrobenzoic acid		
1·212	230·9	1·22
0·8441	252·4	1·21
0·5933	272·8	1·21
0·5304	278·7	$1·20_5$
0·5208	280·6	$1·22_5$
0·4528	288·0	$1·22_5$
0·3866	296·4	1·24
0·3802	296·1	$1·21_5$
0·2004	322·8	1·20
	$\Lambda_0 = 370·4$	
2,6-Dihydroxybenzoic acid		
2·144	370·5	150 *
1·277	376·4	106
1·185	375·6	81·9
0·8367	378·6	107
0·8301	378·4	97·8
0·5187	379·8	77·0
0·5099	380·0	80·9
0·4141	380·2	63·5
0·2974	381·2	102·3
0·3514	380·9	66·3
0·2761	382·2	107·9
	$\Lambda_0 = 385·6$	
2,4-Dichlorobenzoic acid		
0·5170	307·2	2·08
0·4902	309·6	2·08
0·4594	313·3	$2·12_5$
0·4413	313·2	$2·04_5$
0·3741	320·8	$2·10_5$
0·3394	324·8	$2·13_5$
0·3285	325·5	$2·10_5$
0·2247	337·1	2·10
0·2200	336·2	1·99
0·1580	346·0	2·14
	$\Lambda_0 = 371·0$	

10^3C	Λ	10^3K
2,4-Dihydroxybenzoic acid		
5·127	102·5	0·47
2·701	133·3	0·47
2·436	138·3	0·47
1·851	153·9	9·47
1·326	173·6	0·47
1·138	183·0	0·47
1·093	185·5	0·47
0·8056	204·7	0·47
0·6310	220·7	0·47
0·4812	237·9	0·47
0·4152	246·8	0·46
0·2933	269·4	0·47
	$\Lambda_0 = 385·0$	
3,4-Dihydroxybenzoic acid		
1·623	49·23	0·0323
1·130	58·30	0·0326
1·035	60·46	0·0323
0·8840	64·94	0·0323
0·6331	75·41	0·0324
0·5433	80·59	0·0323
0·5387	81·05	0·0322
0·4436	88·17	0·0325
0·3240	100·7	0·0324
0·2757	107·9	0·0326
0·2281	116·1	0·0322
	$\Lambda_0 = 370·6$	
2,5-Dichlorobenzoic acid		
0·8766	307·8	3·39
0·5145	329·7	3·50
0·4641	330·7	3·24
0·3938	338·7	3·59
0·3468	341·9	3·56
0·2157	351·4	3·40
0·1631	356·1	3·38
0·1539	356·4	3·25
	$\Lambda_0 = 373·9$	

10^3C	Λ	10^3K
2,5-Dihydroxybenzoic acid		
2·687	180·1	1·11
1·624	212·4	1·13
1·430	219·6	$1·11_5$
1·087	237·1	$1·11_5$
1·075	238·3	$1·12_5$
0·9254	248·2	$1·13_5$
0·7338	262·4	$1·13_5$
0·5460	279·4	$1·12_5$
0·5357	279·7	$1·11_5$
0·4817	285·3	$1·10_5$
0·3535	302·1	$1·11_5$
0·2800	313·0	$1·11_5$
	$\Lambda_0 = 378·4$	
3,5-Dihydroxybenzoic acid		
1·607	80·17	0·0913
1·336	86·93	0·0915
1·056	96·13	0·0915
0·9917	98·67	0·0914
0·8279	106·4	0·0914
0·8276	106·5	0·0916
0·6968	114·2	0·0913
0·6494	117·5	0·0909
0·4760	132·9	0·0914
0·4215	139·3	0·0914
	$\Lambda_0 = 374·4$	
2,6-Dichlorobenzoic acid		
2·199	346·6	$24·9_5$
1·636	353·8	$26·0_5$
1·111	360·1	$25·6_5$
1·042	361·3	26·3
0·8238	364·4	26·8
0·6937	365·5	$24·4_5$
0·5340	367·9	24·2
0·4844	369·0	25·4
0·4062	370·1	$24·6_5$
0·3892	370·8	$26·5_5$
	$\Lambda_0 = 378·7$	

* This measurement was not used in the evaluation of Λ_0 or in calculating K.

One of us (L. G. B.) thanks the Governing Body of Chelsea College of Science and Technology for a Research Assistantship.

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LONDON, S.W.3.

[*Received, December 3rd*, 1958.]

[6] Dippy, Hughes, and Laxton, *J.*, 1954, 1470.
[7] Ives, *J.*, 1933, 731.
[8] Ives and Sames, *J.*, 1943, 511.

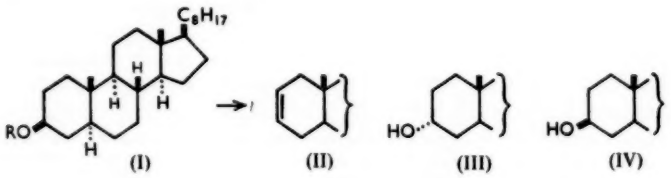
XUM

340. *Preparation of Axial Alcohols and Olefins from Equatorial Alcohols.*

By G. H. Douglas, P. S. Ellington, G. D. Meakins, and R. Swindells.

Cases in which the toluene-*p*-sulphonate of an equatorial alcohol is decomposed by contact with alumina to a mixture of the epimeric axial alcohol and an olefin are recorded (*e.g.*, cholestanyl toluene-*p*-sulphonate ⟶ cholestan-3α-ol and cholest-2-ene). The proportion of axial alcohol to olefin varies with the type of alumina used, thus giving convenient preparations of both products.

While cyclic alcohols with equatorial hydroxyl groups can generally be obtained by reduction of the corresponding ketones with dissolving metals or by equilibration of the axial epimers, preparation of the axial alcohols has frequently been troublesome. Catalytic reduction of a ketone in acidic media usually gives a preponderance of the axial isomer, but the ratio of equatorial to axial product varies widely with the keto-group's environment [1,2] and in some cases with the nature of the catalyst.[3] When reducible C=C bonds are present, chemical reduction of the ketone must be used. Recent investigations [2,4] have confirmed the generalisation [1] that reduction of highly hindered ketones with various hydrides gives mainly the axial alcohols, but with less hindered ketones prediction of the major product is difficult. In some important cases, such as 3-oxo-steroids and -triterpenes, reduction with hydrides or with agents of higher steric requirements (*e.g.*, aluminium alkoxides [5]) leads predominantly to the equatorial alcohols.



(I) (II) (III) (IV)

In work on steroids with unnatural stereochemistry [6] a method was required for converting 3β(equatorial)-alcohols into the 3α-epimers without proceeding through the related 3-ketones. The use of the sulphonic esters of the 3β-alcohols appeared promising since the ready elimination of the sulphonyloxy-group gives mixtures of olefins and derivatives of the epimeric alcohols. To evaluate the merits of various methods (see Table) the toluene-*p*-, *p*-bromophenyl-, and methane-sulphonic esters (I) of cholestan-3β-ol (IV) were studied. [The yields in the Table correspond to the weights of materials in the fractions obtained by chromatographic separation of the mixed products. These materials were characterised by their infrared spectra, and with one exception (see below) crystallisation gave products with satisfactory constants in greater than 70% recovery.]

By method 1 (acetolysis), cholest-2-ene (II) was the major product as recorded previously for the cholestanyl toluene-*p*-sulphonates,[7] and use of aqueous dimethylformamide as solvent [8] did not increase the yield of cholestan-3α-ol (III). This is to be

[1] Barton, *J.*, 1953, 1027.
[2] Dauben, Blanz, Jiu, and Micheli, *J. Amer. Chem. Soc.*, 1956, **78**, 3752.
[3] Djerassi, Manson, and Gorman, *ibid.*, 1955, **77**, 4925.
[4] Dauben, Fonken, and Noyce, *ibid.*, 1956, **78**, 2579; Henbest and Wilson, *J.*, 1956, 3289; Wicker, *J. Amer. Chem. Soc.*, 1958, **80**, 640.
[5] Biedeback, *Arch. Pharm.*, 1943, **281**, 49.
[6] Castells, Jones, Meakins, and Williams, *J.*, 1959, 1159, and unpublished work.
[7] King and Bigelow, *J. Amer. Chem. Soc.*, 1952, **74**, 3338.
[8] Bharucha, Buckley, Cross, Rubin, and Ziegler, *Canad. J. Chem.*, 1956, **34**, 982.

contrasted with methanolysis of the toluene-*p*-sulphonate [9,10] which gives 3α-methoxycholestane (75%) and cholest-2-ene (25%). Alcoholysis with allyl alcohol and reductive fission of the products (mainly cholest-2-ene and cholestan-3α-yl allyl ether) with lithium in ethylamine (method 2) led to somewhat higher yields of cholestan-3α-ol. This method, however, required very careful control of the experimental conditions, and with the esters of 5α-lumist-7-en-3β-ol [6] considerable amounts of the 3β-alcohol were formed.

Method 3, the most successful, is a one-stage process involving decomposition of the

Reactions of Cholestan-3β-yl Esters (yields to nearest 5%).

Ester group, R	Δ²-Compound	3α-Alcohol	3β-Alcohol	Unchanged
Method 1. Ester boiled with KOAc–AcOH, product saponified with KOH–EtOH.				
p-$C_6H_4Me\cdot SO_2$	55	35	—	—
p-$C_6H_4Br\cdot SO_2$	60	30	—	—
$Me\cdot SO_2$	60	25	5	—
Method 2. Ester boiled with $CH_2{:}CH\cdot CH_2\cdot OH$–$C_6H_6$, product treated with Li–$EtNH_2$.				
p-$C_6H_4Me\cdot SO_2$	40	50	—	—
p-$C_6H_4Br\cdot SO_2$	45	50	—	—
$MeSO_2$	45	45	—	—

Method 3. Ester in benzene adsorbed on a column of alumina.

Ester group, R	Type of alumina *	Contact time (hr.)	Δ²-Compound	3α-Alcohol	3β-Alcohol	Unchanged
p-$C_6H_4Me\cdot SO_2$ ...	*a*, *b*	18	70	25	5	—
,, ...	*c*, *d*, *e*	18	—	—	—	100
,, ...	*f*	18	65	35	—	—
p-$C_6H_4Br\cdot SO_2$ ...	*f*	18	65	30	—	—
$Me\cdot SO_2$	*f*	18	65	25	10	—
p-$C_6H_4Me\cdot SO_2$ ...	*g*	42	25	35	—	35
,, ...	*g*	66	40	60	—	—
p-$C_6H_4Br\cdot SO_2$ ...	*g*	66	50	45	—	—
$Me\cdot SO_2$	*g*	66	55	35	5	—

* Types *a* and *b* were untreated P. Spence's Grades O and H alumina respectively. Type *c* was prepared by shaking Grade H material (1 kg.) for 12 hr. with 10% aqueous acetic acid (50 c.c.). Type *d* was obtained by stirring Grade H material with an excess of ethyl acetate at 20° for 2 days, filtering it, washing it repeatedly with hot water, and drying it at 250° for 2 days. Type *e* was prepared by shaking Grade H material (1 kg.) for 12 hr. with a solution of potassium hydroxide (100 g.) in water (75 c.c.). Type *f* was Grade O material heated at 250° for 2 days. Type *g* was obtained by heating type *e* at 250° for 2 days.

esters on alumina.* In the few available analogies [9,11,12] inverted alcohols (up to *ca.* 30% yield) have been obtained from toluene-*p*-sulphonates by using slightly damp or alkaline alumina. The experiments summarised in the Table show that cholestan-3α-ol is best obtained (60% yield) from the 3β-toluene-*p*-sulphonate (rather than the other two esters) by contact with alumina previously impregnated with potassium hydroxide and dried at 250°. In practice the method involves adsorption of the ester on to a column of alumina which is left for 3 days and then developed with solvents in the standard chromatographic sequence. Ergosta-7,22-dien-3α-ol and several axial alcohols in the lumisterol series [6] were prepared (*ca.* 60% yields) in this way.

The proportion of axial alcohol to olefin varies with the type of alumina used: with untreated alumina cholest-2-ene is the major product (70% yield) from cholestanyl toluene-*p*-sulphonate. Comparable yields of Δ²-compounds were similarly obtained from the toluene-*p*-sulphonates of ergosta-7,22-dien-3β-ol, 3β-hydroxyergost-7-en-11-one, lupeol,

* We are indebted to Dr. A. Nickon for drawing our attention to the preparation of cholestan-7α-ol [11] by this method and for providing unpublished details of a further example.[12]

[9] Clayton, Henbest, and Smith, *J.*, 1957, 1982.
[10] Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937.
[11] Cremlyn and Shoppee, *J.*, 1954, 3515.
[12] 3α-Hydroxyallopregnan-3α-ol-20-one is formed in 25% yield from the corresponding 3β-toluene-*p*-sulphonate with slightly damp alumina (unpublished work by Dr. A. Nickon).

and β-amyrin. (In the two steroids the positions of the double bonds in ring A were not investigated, but the tentative Δ^2-formulations are more probable than the alternative Δ^3-structures.[9]) α-Amyrin toluene-*p*-sulphonate gave unsaturated material (75%) as a glass having an infrared spectrum almost identical with that of pure ursa-2,12-diene (α-amyrilene II).[13] The low yield (35%) finally obtained is thus probably due to the difficulty in crystallising this compound rather than to skeletal rearrangement [14] during the treatment with alumina.

After completion of this work the preparation of cholestan-3α-ol in high yield from cholestanyl toluene-*p*-sulphonate and dimethylformamide was briefly reported.[15]

Experimental

For general directions see *J.*, 1958, 2156.

Cholestan-3β-yl Esters.—A solution of cholestan-3β-ol (1 mol.) and the appropriate sulphonyl chloride (2 mol.) in an excess of pyridine (*ca.* 20 mol.) was kept at 0° for 24 hr. After dilution with water and filtration the product was washed with a little ethanol and crystallised from ethanol. The toluene-*p*-sulphonate had m. p. 133—135°, $\nu_{max.}$ 1189 and 1176 cm.$^{-1}$: the p-*bromobenzenesulphonate* had m. p. 120—122° (Found: C, 65·4; H, 8·6. $C_{33}H_{51}O_3SBr$ requires C, 65·2; H, 8·5%), $\nu_{max.}$ 1188 and 1175 cm.$^{-1}$: the *methanesulphonate* had m. p. 108—110° (Found: C, 72·3; H, 10·9. $C_{28}H_{50}O_3S$ requires C, 72·1; H, 10·8%), $\nu_{max.}$ 1189 and 1177 cm.$^{-1}$.

Reaction of Cholestan-3β-yl Esters.—(a) *With potassium acetate in acetic acid.* A solution of the toluene-*p*-sulphonate (1 g.) and potassium acetate (1 g.) in acetic acid (20 c.c.) was refluxed for 9 hr., then evaporated *in vacuo*. The residue was extracted with ether, and the ether solution dried and evaporated. The material (720 mg.) so obtained was refluxed with 5% ethanolic potassium hydroxide (20 c.c.) for 2 hr. and the product (660 mg.) was adsorbed on alumina (60 g.; Grade O). Elution with benzene (200 c.c.) gave cholest-2-ene (360 mg.), m. p. 74—75° after crystallisation from methanol, $[\alpha]_D$ +66° (*c* 0·5), identified by mixed m. p. and comparison of infrared spectra with an authentic specimen and by conversion into the dibromide,[16] m. p. 124—125°, $[\alpha]_D$ +64° (*c* 1·5).

Elution with ether–methanol (19 : 1; 300 c.c.) gave cholestan-3α-ol (260 mg.), m. p. 184—186° (from ethanol), $[\alpha]_D$ +23° (*c* 0·8), $\nu_{max.}$ 1037 (weak) and 1003 cm.$^{-1}$. (The peak at 1037 cm.$^{-1}$ was still present after purification through the 3 : 5-dinitrobenzoate, m. p. 160—161°. This band complicates analysis of cholestan-3β-ol–cholestan-3α-ol mixtures by infrared spectroscopy.) Further elution with ether–methanol (4 : 1) did not yield cholestan-3β-ol.

Similar treatment of cholestan-3β-yl *p*-bromobenzenesulphonate (1 g.) gave cholest-2-ene (360 mg.) and cholestan-3α-ol (190 mg.). The methanesulphonate (1 g.) afforded cholest-2-ene (490 mg.), cholestan-3α-ol (210 mg.), and cholestan-3β-ol (40 mg.), m. p. 142—143°, $[\alpha]_D$ +22° (*c* 1·0), $\nu_{max.}$ 1038 cm.$^{-1}$.

(b) *With allyl alcohol.* A solution of the toluene-*p*-sulphonate (1 g.) in dry allyl alcohol–benzene (1 : 1; 200 c.c.) was boiled for 48 hr. After repeated washing with water the benzene solution was dried, filtered through alumina (100 g.; Grade H), and evaporated. The residue was dissolved in anhydrous ethylamine–liquid ammonia (1 : 1; 100 c.c.), and lithium was added until the solution remained blue. After addition of methanol and then 4N-hydrochloric acid the mixture was extracted with ether. The material so obtained was chromatographed (as above) to give cholest-2-ene (290 mg.) and cholestan-3α-ol (390 mg.).

The *p*-bromobenzenesulphonate (1 g.) and the methanesulphonate (1 g.) similarly afforded cholest-2-ene (275 and 355 mg.) and cholestan-3α-ol (320 mg. and 405 mg. respectively).

(c) *With various types of alumina.* The general procedure was as follows. The ester (1 g.) in benzene (30 c.c.) was adsorbed on a column of the appropriate alumina (see Table; 100 g.). More benzene (10 c.c.) was run on to the column which was then stoppered for the required time.

[13] Dieterle, Brass, and Schaal, *Arch. Pharm.*, 1937, **275**, 557; Winterstein and Stein, *Annalen*, 1933, **502**, 223.
[14] Noller, *J. Amer. Chem. Soc.*, 1950, **72**, 625; Burns, Cole, Parkes, and White, *Austral. J. Chem.*, 1956, **9**, 406.
[15] Chang and Blickenstaff, *J. Amer. Chem. Soc.*, 1958, **80**, 2906.
[16] Barton and Rosenfelder, *J.*, 1951, 1048.

Elution with benzene (300 c.c.) gave cholest-2-ene and, in some cases, unchanged ester. (These compounds were separated by a separate chromatograph on Grade O alumina with pentane and pentane–benzene for elution.) The epimeric cholestanols were then eluted with ether–methanol as described above.

Preparation of 3α-*Alcohols.*—The following example illustrates the general procedure. A solution of ergosta-7,22-dien-3β-ol (1 g.; m. p. 174—175°) and toluene-*p*-sulphonyl chloride (1 g.) in pyridine (5 c.c.) was kept at 0° for 24 hr. The toluene-*p*-sulphonate, isolated by dilution with water and filtration, was washed with a little ethanol, dried *in vacuo*, and crystallised from ethyl acetate–methanol. The product (1·2 g.; m. p. 175—177°, $[\alpha]_D$ −21°, not analysed) was adsorbed on alumina [100 g., type (*g*) of Table] as described above. After 66 hr. the column was eluted with benzene (300 c.c.) to give *ergosta*-2(?),7,22-*triene* (360 mg.), m. p. 115—118° after crystallisation from ethyl acetate–methanol, $[\alpha]_D$ +0·6° (*c* 1·6) (Found: C, 88·6; H, 11·6. $C_{28}H_{44}$ requires C, 88·35; H, 11·65%). Ether–methanol (19 : 1; 350 c.c.) eluted ergosta-7,22-dien-3α-ol (590 mg.), m. p. 208—211° (from acetone), $[\alpha]_D$ +5° (*c* 1·2). (This m. p. is lower than that, 215—216°, previously recorded.[17] Infrared analysis showed that our product was free from any 3β-ol, and acetylation afforded an acetate with m. p. 154—156°, $[\alpha]_D$ +4° (*c* 0·9), in agreement with the literature.[17]

Similar experiments with lumisterol derivatives will be described later.[6]

Preparation of Ring A *Olefins.*—The preceding experiment on ergosta-7,22-dien-3β-ol (1 g.) was repeated, and the toluene-*p*-sulphonate decomposed by treatment with Grade H alumina for 18 hr. Elution with benzene (300 c.c.) gave the ergostatriene (720 mg.), m. p. 116—118° after crystallisation.

3β-Hydroxyergost-7-en-11-one (1 g.) similarly gave a toluene-*p*-sulphonate, m. p. 157—159°, and thence *ergosta*-2(?),7-*dien*-11-*one* (725 mg.), m. p. 113—114° (from acetone), $[\alpha]_D$ +81° (*c* 2·1) (Found: C, 84·4; H, 11·2. $C_{28}H_{44}O$ requires C, 84·8; H, 11·2%).

β-Amyrin (1 g.) yielded an olefinic fraction (705 mg.) which was crystallised from acetone and then ethyl acetate–methanol, to give oleana-2,12-diene (β-amyrilene II; Winterstein *et al.*[13]) (550 mg.), m. p. 148·5—150°, $[\alpha]_D$ +140° (*c* 1·4). Lupeol (1 g.) gave olefinic material (700 mg.) from which lupa-2,20(29)-diene [18] (580 mg.), m. p. 164—166°, $[\alpha]_D$ +57° (*c* 2·3), was obtained by crystallisation from ethyl acetate. Decomposition of the toluene-*p*-sulphonate from α-amyrin (1 g.) gave an olefinic fraction (760 mg.) which was chromatographed on alumina (100 g.; Grade O). Elution with pentane (5 × 20 c.c.) gave fractions which slowly solidified in contact with acetone. The combined solids were crystallised from acetone, to give ursa-2,12-diene (α-amyrilene II) (340 mg.), m. p. 116—118°, $[\alpha]_D$ +135° (*c* 1·0).

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The University, Manchester, 13.
Dyson Perrins Laboratory, Oxford. [*Received, December 15th,* 1958.]

[17] Windaus, Dithmar, Murke, and Suckfüll, *Annalen*, 1931, **488**, 91.
[18] Biedebach, *Arch. Pharm.*, 1939, **277**, 163.

XUM

341. *The Homolytic Methylation of Naphthalene.*

By J. A. Kent and R. O. C. Norman.

The reaction of naphthalene with the free methyl radical has been investigated, di-*tert.*-butyl peroxide being used as the source of methyl radicals. The ratio of the amounts of the two methylnaphthalenes formed has been determined at various temperatures, from which the differences in activation energies and entropies for reactions at the α- and the β-positions of the naphthalene nucleus have been calculated. An analysis of the importance of the steric hindrance to α-substitution and of the difference in polarisability of the α- and the β-positions has been made in the light of these results.

It has been predicted by molecular-orbital theory [1] that naphthalene should be more reactive in the α-position than in the β-position towards free radicals. This prediction has been confirmed for the phenylation of naphthalene by the free phenyl radical, the α-position proving to be about four times as reactive as the β-position.[2,3] A more detailed treatment of this problem necessitates two refinements: first, an evaluation of the difference in electronic polarisability in the α- and the β-position, for comparison with theoretical quantities such as the difference in atom-localisation energies: secondly, an evaluation of the steric hindrance to substitution at the α-position by the *peri*-hydrogen atom.

With these objects, the α/β ratio of methylnaphthalenes formed by the attack of the free methyl radical on naphthalene has been measured over a range of temperatures, and from the results have been calculated the differences in activation energies, $\Delta H^{\ddagger}$, and in activation entropies, $\Delta S^{\ddagger}$, between reactions at the α- and the β-position. The methyl radicals were generated by the decomposition of di-*tert.*-butyl peroxide at the temperatures at which the reaction was being investigated.

Experimental

Reaction of Methyl Radicals with Naphthalene.—Di-*tert.*-butyl peroxide (5 g.) was added to a solution of naphthalene (5 g.) in chlorobenzene (100 ml.). The solution was heated on a water-bath at 98° for 3 weeks (about twice the half-life of the peroxide at this temperature), *tert.*-butyl alcohol and acetone being removed (through a short fractionating column) as formed, in order to keep the temperature constant. The remaining volatile materials and chlorobenzene were removed by fractional distillation and the residue was examined by gas chromatography.

In later experiments, at different temperatures, di-*tert.*-butyl peroxide (5 g.) and naphthalene (5 g.) in the appropriate solvent (100 ml.) were refluxed together for approximately five times the half-life of the peroxide at this temperature. The solvents used were chlorobenzene, bromobenzene, and *o*-dichlorobenzene. The procedure employed was that described above for the reaction at 98°.

The reaction at 156° was repeated with 7·5, 2·5, 1·0, and 0·5 g. of di-*tert.*-butyl peroxide severally. The methylnaphthalenes produced were analysed by gas chromatography as described below: the ratio of α- to β-methylnaphthalene remained constant, within experimental error, throughout this set of experiments (see Table 2).

Gas Chromatography.—The column (497 cm. × 4·5 mm.) was packed with 24·8% apiezon L coated on firebrick and operated at 179° with a carrying stream of hydrogen (70 ml./min.), a slightly increased inlet pressure (25 lbs./in.^{2}) and atmospheric pressure at the outlet. A hydrogen-flame detector was employed, coupled to a Honeywell Brown recorder which gave a linear response. Under these conditions the peaks due to α- and β-methylnaphthalene were completely resolved, their retention times being 53½ and 45 min. respectively. The column yielded 3750 theoretical plates.

[1] "Progress in Organic Chemistry," ed. by J. W. Cook, Butterworths, London, 1953, Vol. II, p. 23; Wheland, *J. Amer. Chem. Soc.*, 1942, **64**, 900.
[2] Huisgen and Grashey, *Annalen*, 1957, **607**, 46.
[3] Marshall and Waters, *J.*, 1959, 381.

The injection of standard mixtures of α- and β-methylnaphthalene showed that the ratio of the peak areas was proportional to the ratio of quantities of the two materials, the areas being measured by constructing triangles made up of tangents to the Gaussian curves and the intercepts on the base-line. 0·5—0·6 ml. of the reaction mixture was injected, this quantity containing enough α-methylnaphthalene to give almost full-scale deflection on the recorder (*ca.* 0·03 ml.). A large peak due to unchanged naphthalene (approximately 90% of the reaction mixture) was recorded first, followed by β- and then α-methylnaphthalene. The experiment in *o*-dichlorobenzene yielded a fourth peak of retention time consistent with its being for a methylated *o*-dichlorobenzene.

Comparison of the ratio of materials in standard mixtures with the ratio of areas of the chromatographic peaks showed that the analysis was accurate to 3%.

The results of methylation experiments carried out at 98—179° are recorded in Table 1. Table 2 records the α/β ratios obtained at a constant temperature with different concentrations of peroxide.

TABLE 1. *Variation of α : β ratio of methylnaphthalenes with temperature.*

Solvent	PhCl	PhCl	PhBr	o-$C_6H_4Cl_2$
Temp.	98°	132°	156°	179°
No. of expts.	4	3	3	6
Mean α : β ratio	5·3	3·8	2·9	2·7

TABLE 2. *Variation of α : β ratio of methylnaphthalenes with peroxide concentration.*

Peroxide (g.)	7·5	5·0	2·5	1·0	0·5
Wt. ratio of peroxide : naphthalene	1·5	1·0	0·5	0·2	0·1
No. of expts.	2	3	2	2	2
α : β ratios	3·0, 2·9	2·8, 2·9, 2·9	3·1, 3·0	3·0, 2·9	2·9, 2·9
Mean α : β ratio	2·95	2·90	3·05	2·95	2·90

DISCUSSION

One possible source of error in using the ratio of α- to β-methylnaphthalene as a measure of the relative reactivity of the α- and the β-position of naphthalene was that the two methylnaphthalenes might themselves react with methyl radicals, either in the aromatic nucleus or in the side chain, and to unequal extents. An experiment in which a mixture of α- and β-methylnaphthalenes was attacked by methyl radicals showed that the α-compound was the more reactive, so that further reaction on these products was a real source of error. However, experiments in which decreasing quantities of di-*tert.*-butyl peroxide were employed to react with naphthalene showed that the α : β ratio did not change, within experimental error, with the amount of reaction on naphthalene. Evidently the amount of reaction on naphthalene was always so small that further reaction of the two main products was negligible.

The possibility that the change in the α : β ratio reflects a change in the selectivity of the methyl radical in different solvents rather than, or in addition to, relative changes in rate due to activation energy and entropy differences has also to be considered. Thus, Russell has found that the effective reactivity of a chlorine atom is altered considerably by change of solvent, there appearing to be some type of complex formation between chlorine atoms and aromatic solvents.[4] Such an effect did not seem to be operative here, since the largest variation in the α : β ratio occurred when the aromatic solvent in two cases was kept constant (chlorobenzene) and only the temperature was varied. Furthermore, the changes in α : β ratio were large compared with the corresponding changes for phenylation of naphthalene with different solvents.[2] It is probable that any alteration in the reactivity of the methyl radical in these experiments was small; certainly the much smaller effect of complex formation on the phenyl radical [2] than on the chlorine atom [4] is consistent with this. It may be that such complex formation is important only when the accepting atom or radical is one of high electronegativity.

[4] Russell, *J. Amer. Chem. Soc.*, 1957, **79**, 2977.

A treatment based on transition-state theory shows that:

$$\ln (k_\alpha/k_\beta) = \Delta S^\ddagger(\alpha - \beta)/\boldsymbol{R} - \Delta H^\ddagger(\alpha - \beta)/\boldsymbol{R}T$$

where k_α, k_β are the velocity constants for methylation at the α- and β-position. The ratio of the quantities of α- and β-methyl derivatives are, in this case, a measure of the relative rate constants, and so $k_\alpha/k_\beta = \alpha/\beta$. Therefore from the plot of ln (α/β) against the reciprocal of the absolute temperature, the gradient gives $\Delta H^\ddagger$ and the intercept on the ln (α/β) axis gives $\Delta S^\ddagger$. The values obtained from the linear graph were: $\Delta H^\ddagger(\alpha - \beta) = -3{\cdot}4$ kcal./mole; $\Delta S^\ddagger(\alpha - \beta) = -5{\cdot}6$ e.u. The difference in activation energies, $\Delta H^\ddagger(\alpha - \beta)$, depends on both the difference in polarisability of the α- and the β-position and the non-bonding steric interaction between the *peri*-hydrogen atom and the α-methyl group.

It is not possible cleanly to separate these two quantities, but an estimate has been made [5] of the non-bonding steric interaction in α-methylnaphthalene itself of 1·6 kcal./mole. Scale models suggest that the interaction will be somewhat less in the transition state concerned in the present investigation, so that 1·6 kcal./mole provides an upper limit for this interaction. This value, coupled with the experimental value for $\Delta H^\ddagger$, indicates a difference in π-electron-excitation energies of the α- and the β-position of about −5 kcal./mole.

A model frequently used for the transition state in an aromatic substitution is one in which the aromatic carbon atom under attack has become bonded to the reagent and has changed its hybridisation from sp^2 to sp^3, being removed from conjugation with the remainder of the aromatic system. For the difference in π-electron-excitation energies between the α- and the β-position in naphthalene in the attainment of such a transition state a theoretical value of 0·31β has been obtained, where β is the resonance integral.[1] β has the approximate value of −20 kcal./mole for aromatic hydrocarbons such as naphthalene,[6] whence the theoretical difference in excitation energies of the α- and the β-position is approximately −6 kcal./mole. Our experimental upper-limit value, −5 kcal./mole, is significantly less than this, and may indicate that the transition state in the methylation is one in which the aromatic carbon atom undergoing attack is not fully bonded with the methyl radical and is still partially conjugated with the rest of the aromatic system. This reasoning accords with that of Dewar *et al.* who proposed similar models for the transition states in aromatic nitration [7] and chlorination,[8] and suggested that the structure of the transition state depends on the nature of the reagent.[8]

It is difficult to draw positive conclusions from the difference in activation entropies for reaction at the α- and the β-position, for $\Delta S^\ddagger$ has often been found to be a function of $\Delta H^\ddagger$. Nevertheless the difference is in accord with the possibility that, in addition to the non-bonding strain, there is restriction to rotation of the methyl group in the transition state for methylation at the α-position.

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[5] Packer, Vaughan, and Wong, *J. Amer. Chem. Soc.*, 1958, **80**, 905.
[6] Wheland, *J. Amer. Chem. Soc.*, 1941, **63**, 2025.
[7] Dewar, Mole, and Warford, *J.*, 1956, 3581.
[8] Dewar and Mole, *J.*, 1957, 342.

342. *Synthesis of 3-Substituted Phenanthrenes. The Course of Intramolecular Cyclisation of 2-(m-Substituted Phenyl)cyclohexylacetic Acids.*

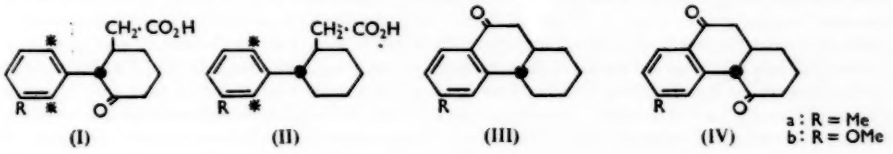
By Shlomo Bien and Miriam Boazi.

2-*m*-Tolyl- and 2-*m*-methoxyphenyl-cyclohexylacetic acid and their 3-oxo-derivatives cyclise intramolecularly to afford octahydrophenanthrene derivatives, shown by conversion into 3-substituted phenanthrenes to bear a methyl or a methoxyl group exclusively in one position. The compounds submitted to cyclisation are accessible through Michael condensation of 2-arylcyclohex-2-enones with malonic esters followed by standard transformations.

2-Arylcyclohexylacetic acids and their 3-oxo-derivatives have been used as precursors of hydrophenanthrenes.[1,2] In all of these cases only one position was open to attack in the intramolecular Friedel–Crafts reaction.

Since in *meta*-substituted analogues (I, II) there are two positions (marked *) open to such attack, it seemed of interest to determine experimentally the course of their reaction.

2-*m*-Tolyl- and 2-*m*-methoxyphenyl-cyclohex-2-enone were submitted to Michael condensation with t-butyl malonate. The products were hydrolysed and decarboxylated, giving compounds of type (I) which were reduced by the Huang-Minlon procedure [3] to compounds of type (II). Cyclisation of the product (I) or (II) with anhydrous hydrogen



fluoride gave octahydropenanthrenes (IV, III) in high yields. Further treatment in each case gave solely 3-methylphenanthrene or 3-methoxyphenanthrene.

It is thus clear that intramolecular cyclisation occurred at one position, *viz.*, *para* to the substituent in the phenyl nucleus. No isomeric phenanthrenes were isolated despite careful chromatography.

In the practically quantitative intramolecular cyclisations of 3-oxo-2-*o*-tolylcyclohexylacetic acid [2] and 3-oxo-2-(2,3-dimethoxyphenyl)cyclohexylacetic acid [4] the position attacked is *meta* with reference to an *ortho-para*-directing group. It therefore appears that the reason for the apparently exclusive attack of the position *para* to the methyl or the methoxyl group in the compounds described in this paper is preponderantly a steric one.

Experimental

1-m-*Tolylcyclohexene*.—To *m*-tolylmagnesium bromide, prepared from *m*-bromotoluene (20 g., 0·11 mole) and magnesium (2·7 g., 0·11 g.-atom) in dry ether (120 ml.), cyclohexanone (11·4 g., 0·11 mole) in dry ether (11 ml.) was added with stirring at room temperature. The complex began to be precipitated before addition was complete. The mixture was then refluxed for 1 hr., kept overnight, and decomposed with saturated ammonium chloride solution. The ether layer was dried and the solvent removed. The residual oil was boiled with anhydrous oxalic acid (3·8 g.) in toluene (95 ml.) until no more water was obtained in an azeotropic collector.[5] The usual isolation gave the cyclo-olefin, b. p. 76—78°/0·07 mm. (16 g., 80%).

2-m-*Tolylcyclohex-2-enone Oxime*.—To a solution of 1-*m*-tolylcyclohexene (6·05 g., 0·03 mole)

[1] Bachmann and Fornefeld, *J. Amer. Chem. Soc.*, 1950, **72**, 5529.
[2] Klibansky and Ginsburg, *J.*, 1957, 1293.
[3] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.
[4] Elad and Ginsburg, unpublished results.
[5] Bergmann, Pappo, and Ginsburg, *J.*, 1950, 1369.

in acetic acid (6·5 ml.) cold n-pentyl nitrite (4·7 g., 0·04 mole) was added. The mixture was cooled to −15°, and concentrated hydrochloric acid (4·0 ml.) was then added dropwise with stirring at this temperature. The addition was complete in about 30 min., but stirring was continued for a further 2 hr. at −10°. The nitrosochloride was filtered off with suction, washed with ice-cold ethanol, and dried [5·7 g.; m. p. 118—121° (decomp.)]. The nitrosochloride was immediately converted into the oxime by slowly warming its suspension in pyridine (20 ml.) to 75°. After 10 min. all of the solid had dissolved. The solution was cooled and excess of hydrochloric acid was added. The precipitated oxime was filtered off, washed with water, and dried (5·5 g., 77%). The pure *oxime* had m. p. 107° (from ethanol) (Found: C, 76·9; H, 7·2; N, 6·9. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5; N, 6·9%).

2-m-*Tolylcyclohex-2-enone*.—The crude oxime (20 g., 0·1 mole), concentrated hydrochloric acid (20 ml.), and water (150 ml.) were refluxed for 3 hr. After cooling, the free ketone was taken up in ether, and the extract washed with 5% sodium carbonate solution, then water, and dried (Na_2SO_4). After removal of solvent, the residue was distilled in a vacuum. The unsaturated *ketone* had b. p. 123—125°/0·5 mm. (10 g., 55%), $\nu_{max.}$ (in $CHCl_3$), 1680 cm.$^{-1}$ (C:C·C:O).

The red 2 : 4-*dinitrophenylhydrazone* had m. p. 163° (from ethanol–ethyl acetate) (Found: C, 61·8; H, 4·95; N, 15·3. $C_{19}H_{18}O_4N_4$ requires C, 62·3; H, 4·95; N, 15·3%). The colourless *semicarbazone* had m. p. 203·5—204° (from ethanol) (Found: C, 69·3; H, 6·7; N, 17·1. $C_{14}H_{17}ON_3$ requires C, 69·1; H, 7·0; N, 17·3%).

3-*Oxo*-2-m-*tolylcyclohexylacetic Acid* (Ia).—A mixture of 2-*m*-tolylcyclohex-2-enone (10 g., 0·05 mole), freshly distilled t-butyl malonate (21 g., 0·1 mole) and potassium t-butoxide (from 0·42 g. of potassium and 6·6 ml. of t-butyl alcohol) was kept at 60° for 3 hr., then overnight at room temperature. After acidification with glacial acetic acid, the mixture was taken up in benzene, washed with water until neutral in reaction, and dried (Na_2SO_4). Then naphthalene-β-sulphonic acid (0·15 g.) was added, and the whole refluxed until gas evolution was complete. The cooled solution was extracted with saturated potassium carbonate solution, leaving neutral ester-products in the benzene layer. The benzene was removed and the residue was again saponified as above. The alkaline extracts were combined, acidified with dilute hydrochloric acid, and extracted with ether. The ether was evaporated, and the thick residual oil decarboxylated at 180° until gas evolution was complete. The residue was taken up in saturated sodium carbonate solution and filtered, and the clear solution acidified with dilute hydrochloric acid. Extraction with ether and removal of the solvent gave the viscous monobasic *acid*, which crystallised slowly (7 g., 53%; m. p. 114·5—115·5°, from methylcyclohexane), $\nu_{max.}$ (in $CHCl_3$) 1710 cm.$^{-1}$ (strong broad peak; includes carbonyl C:O and carboxyl C:O) (Found: C, 73·05; H, 7·2; O, 19·4. $C_{15}H_{18}O_3$ requires C, 73·1; H, 7·4; O, 19·5%).

2-m-*Tolylcyclohexylacetic Acid* (IIa).—The keto-acid (Ia) (6·8 g., 0·028 mole) was refluxed with diethylene glycol (75 ml.), potassium hydroxide (6 g.), and 95% hydrazine hydrate (9 ml.) for 2 hr. The condenser was then removed, the temperature was raised to 200°, and the mixture refluxed overnight. The cooled solution was acidified with dilute hydrochloric acid and extracted with chloroform. After the usual working-up the *acid* (4·4 g., 71%) was obtained, having m. p. 122—122·5° (from methanol) (Found: C, 77·0; H, 8·9; O, 14·0. $C_{15}H_{20}O_2$ requires C, 77·55; H, 8·7; O, 13·8%).

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-6-*methyl*-9-*oxophenanthrene* (IIIa).—2-*m*-Tolylcyclohexylacetic acid (5·5 g., 0·024 mole) was treated with anhydrous hydrogen fluoride (*ca.* 200 g.) and after 4 hr. the mixture was worked up in the usual way.[6] From the acidified alkaline extract, starting material was regenerated (0·4 g.). The neutral ketonic material, obtained from the chloroform extract as an oil, crystallised slowly. It recrystallised from ethanol (carbon). The pure ketone (2·6 g.) had m. p. 102—103°. The ethanolic mother-liquor was evaporated to dryness and the residue was taken up in a minimal volume of hexane–benzene (1 : 1) and chromatographed on neutral alumina (50 g.). Elution with benzene gave more (1·45 g.) pure *ketone*, m. p. 103° (from ethanol) (total yield 85%), $\nu_{max.}$ (in $CHCl_3$) 1680 cm.$^{-1}$ (acetophenone-type C:O) (Found: C, 84·1; H, 8·7; O, 7·3. $C_{15}H_{18}O$ requires C, 84·1; H, 8·5; O, 7·5%).

The ketone gave a deep red 2 : 4-*dinitrophenylhydrazone*, m. p. 239—240° (from ethyl acetate) (Found: C, 63·7; H, 5·8; N, 13·7. $C_{21}H_{22}O_4N_4$ requires C, 63·9; H, 5·6; N, 14·2%).

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-9-*hydroxy*-6-*methylphenanthrene* (Va).—To a solution

[6] For leading references cf. "Organic Reactions," Vol. II, pp. 158—162, Wiley, New York, 1949.

of the ketone (IIIa) (1·5 g., 0·007 mole) in methanol (25 ml.) was added sodium borohydride (0·65 g.) at room temperature with stirring. The mixture was set aside overnight and the solvent was evaporated under reduced pressure. Water and dilute hydrochloric acid were added and the mixture was extracted with chloroform. Drying (Na_2SO_4) and evaporation of the solvent gave a quantitative yield of the *alcohol*, m. p. 129—130° (from methylcyclohexane) (Found: C, 82·9; H, 9·7; O, 7·1. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3; O, 7·4%).

3-*Methylphenanthrene*.—The alcohol (Va) (1·43 g.) was dissolved in benzene (75 ml.), naphthalene-β-sulphonic acid (0·02 g.) was added, and the mixture was refluxed for 1 hr. (azeotropic receiver). The cooled solution was washed with water and dried (Na_2SO_4), and the benzene was removed under reduced pressure. The residue (1·3 g.) was dehydrogenated with 30% palladised charcoal (0·15 g.) at 300° for 45 min., then taken up in chloroform and filtered. Removal of the solvent gave colourless prisms, m. p. 65° (from methanol–acetone) (lit.,[7] m. p. 65°).

3-*Methylphenanthraquinone*.—This compound, prepared by Haworth's method,[8] had m. p. 206° (from ethanol). The quinoxaline derivative was obtained as yellow needles, m. p. 210° (from acetic acid) (lit.,[8] m. p. 205—206° and 208°, respectively).

1 : 2 : 3 : 4*a* : 4 : 9 : 10 : 10*a*-*Octahydro*-6-*methyl*-4 : 9-*dioxophenanthrene* (IVa).—Crude 3-oxo-2-*m*-tolylcyclohexylacetic acid (Ia) (2·0 g.) was treated with anhydrous hydrogen fluoride (*ca.* 100 g.). After 4 hr. the mixture was worked up in the usual way. From the acidified potassium carbonate solution starting material was regenerated (0·1 g.), and the ether solution gave an oily residue, which was chromatographed in hexane–benzene (3 : 2) on neutral alumina (75 g.). Elution with the same solvent mixture gave diketone (1·6 g., 89%). No other substance was eluted from the column. The pure *diketone* had m. p. 109° (from methylcyclohexane), $\nu_{max.}$ (in $CHCl_3$) 1710 (alicyclic C:O), 1680 cm.$^{-1}$ (acetophenone-type C:O) (Found: C, 78·8; H, 7·0; O, 14·0. $C_{15}H_{16}O_2$ requires C, 78·9; H, 7·1; O, 14·0%).

The ketone formed a red *bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 209° (from pyridine) (Found: C, 55·8; H, 4·2; O, 21·5; N, 18·7. $C_{27}H_{24}O_8N_8$ requires C, 55·1; H, 4·1; O, 21·75; N, 19·0%).

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-6-*methyl*-4-*oxophenanthrene* (VIa).—The diketone (IVa) (2·1 g.) was hydrogenated in acetic acid (45 ml.) in the presence of 10% palladised carbon (0·3 g.) at an initial hydrogen pressure of 60 lb./sq. in. After hydrogen uptake ceased, the catalyst and the solvent were removed. The oily monoketone was used in the following step without purification. It had $\nu_{max.}$ (in $CHCl_3$) 1710 cm.$^{-1}$ (alicyclic C:O). It formed a yellow 2 : 4-*dinitrophenylhydrazone*, m. p. 193—194° (from ethanol–ethyl acetate) (Found: C, 63·5; H, 5·7; N, 13·4. $C_{21}H_{22}O_4N_4$ requires C, 63·9; H, 5·6; N, 14·2%).

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-6-*methylphenanthrene* (VIIa).—The crude ketone (VIa) (2 g.) was reduced by the Huang-Minlon procedure [9] with potassium hydroxide (2·1 g.), 95% hydrazine hydrate (3·9 ml.), and diethylene glycol (29 ml.). The oily product obtained after the usual working up was chromatographed in light petroleum–benzene (4 : 1) on neutral alumina (100 g.). Elution with the same solvent mixture gave the oily hydrocarbon (1·2 g., 64%), whose infrared absorption shows only C–H bands. The crude compound was used in the next step.

3-*Methylphenanthrene*.—The crude hydrocarbon (VIIa) was dehydrogenated as described above, with 30% palladised carbon, giving 3-methylphenanthrene identical in m. p. and mixed m. p. with the product from the first reaction sequence.

1-m-*Methoxyphenylcyclohexene*.—The olefin was prepared analogously to the *m*-tolyl compound, from *m*-bromoanisole [9] (36·1 g., 0·2 mole), magnesium turnings (4·7 g., 0·2 g.-atom) and cyclohexanone (19 g., 0·2 mole). The crude alcohol was dehydrated as above, giving the *olefin* (40·5 g., 70%), b. p. 106—108°/0·02 mm. (Found: C, 82·7; H, 8·6; O, 8·4. $C_{13}H_{16}O$ requires C, 82·9; H, 8·6; O, 8·5%).

2-m-*Methoxyphenylcyclohex*-2-*enone Oxime*.—The olefin (47·4 g., 0·25 mole) was converted into the oxime as described for the *m*-tolyl compound (90% yield). The pure *oxime* had m. p. 158·5—159·5° (from propan-2-ol) (Found: C, 71·7; H, 6·7; N, 6·4. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 7·0; N, 6·45%).

2-m-*Methoxyphenylcyclohex*-2-*enone*.—The crude oxime (53·5 g., 0·24 mole) was refluxed with dilute hydrochloric acid (48·5 ml. of concentrated acid and 378 ml. of water) for 3 hr. The

[7] Pschorr, *Ber.*, 1906, **39**, 3106.
[8] Haworth, *J.*, 1932, 1125.
[9] Natelson and Gottfried, *J. Amer. Chem. Soc.*, 1939, **61**, 1001.

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usual working up gave the yellow unsaturated *ketone* (21·7 g., 50%), b. p. 140—142°/0·1 mm., $\nu_{max.}$ (in $CHCl_3$) 1675 cm.$^{-1}$ (C:C·C:O). The ketone was characterised as its red 2 : 4-*dinitrophenylhydrazone*, m. p. 170·5—171° (from ethyl acetate) (Found: C, 59·7; H, 4·65; N, 14·7. $C_{19}H_{18}O_5N_4$ requires C, 59·7; H, 4·75; N, 14·65%).

3-*Oxo*-2-m-*methoxyphenylcyclohexylacetic acid* (Ib).—The Michael condensation between the above unsaturated ketone (21·7 g.; 0·1 mole) and t-butyl malonate (47·5 g., 0·22 mole) in the presence of potassium t-butoxide (prepared from 0·84 g. of potassium and 13·2 ml. of t-butyl alcohol) gave a gum (22·2 g., 85%). Trituration with light petroleum induced crystallisation. The crude *acid*, recrystallised twice from 2,2,4-trimethylpentane–benzene, had m. p. 107—108° (Found: C, 68·4; H, 7·0; O, 24·75. $C_{15}H_{18}O_4$ requires C, 68·7; H, 6·9; O, 24·4%). The orange 2 : 4-*dinitrophenylhydrazone* had m. p. 201° (from propan-2-ol) (Found: C, 57·0; H, 5·2; N, 12·7. $C_{21}H_{22}O_7N_4$ requires C, 57·0; H, 5·0; N, 12·7%).

2-m-*Methoxyphenylcyclohexylacetic Acid* (IIb).—The keto-acid (Ib) (15 g., 0·06 mole) was reduced by the Huang-Minlon method [9] with 95% hydrazine hydrate (19·4 ml.), potassium hydroxide (12·9 g.), and diethylene glycol (161 ml.). A thick oil (13·5 g.) was obtained. Infrared absorption showed that partial demethylation occurred during the reduction.[10] For this reason the crude product (5 g.) was methylated in acetone (50 ml.) by alternate addition of methyl sulphate (12 ml.) and potassium hydroxide solution (22·2 g. in 14·8 ml. of water) at 50° with vigorous stirring. Then a distillation head was attached to the flask, the temperature slowly raised to 60°, and the acetone removed by distillation. The mixture was stirred at 60° for 1 hr. and at 95° for another hour. Dilution with water and extraction with ether removed neutral material (0·5 g.). The aqueous solution was acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the solvent gave the acid as a thick syrup (3·9 g.). It was characterised as its S-*benzylthiuronium salt*, m. p. 169° (from aqueous ethanol) (Found: C, 66·75; H, 7·4; N, 6·7. $C_{23}H_{30}O_3N_2S$ requires C, 66·6; H, 7·3; N, 6·75%).

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-6-*methoxy*-9-*oxophenanthrene* (IIIb).—The crude acid (IIb) (2·5 g.) was treated with anhydrous hydrogen fluoride (*ca.* 100 g.) and set aside for 4 hr. A small amount of starting material and only a single neutral ketonic *product* (2 g., 87%) were obtained. This had m. p. 82·5—83° (from 2,2,4-trimethylpentane), $\nu_{max.}$ (in $CHCl_3$) 1675 cm.$^{-1}$ (acetophenone-type C:O) (Found: C, 78·2; H, 8·1; O, 13·7. $C_{15}H_{18}O_2$ requires C, 78·2; H, 7·9; O, 13·9%). The deep red 2 : 4-*dinitrophenylhydrazone* had m. p. 244—245° (from ethyl acetate) (Found: C, 61·85; H, 5·25; N, 13·6; O, 19·2. $C_{21}H_{22}O_5N_4$ requires C, 61·45; H, 5·4; N, 13·65; O, 19·5%).

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-6-*hydroxy*-9-*oxophenanthrene*.—This compound was prepared from the crude product (5 g.), obtained in the Huang-Minlon reduction of (Ib) without remethylation. The usual cyclisation by hydrogen fluoride gave a crude gum (3·7 g.) which on treatment with charcoal in acetic acid gave a pure phenolic ketone (2·3 g.), m. p. 254° (from acetic acid). The acetic acid mother-liquor was evaporated to dryness, and the residue chromatographed in a minimal volume of benzene–hexane (1 : 1) on alumina (65 g.; Fisher). Elution with hexane–benzene (2 : 3) gave the methoxy-ketone (0·7 g.), m. p. 82—83° (from 2,2,4-trimethylpentane), identical in m. p. and mixed m. p. with compound (IIIb). Further elution with chloroform–methanol (19 : 1) gave the phenolic *ketone* (0·6 g.), m. p. 254° (from acetic acid) (Found: C, 77·0; H, 7·4; O, 15·6. $C_{14}H_{16}O_2$ requires C, 77·75; H, 7·5; O, 14·8%).

Methylation of this ketone with methyl sulphate and sodium hydroxide in the usual way gave the methoxy-ketone (IIIb), identical with that described above.

1 : 2 : 3 : 4 : 4*a* : 9 : 10 : 10*a*-*Octahydro*-6-*methoxyphenanthrene* (VIIb).—The ketone (IIIb) (2 g.) was hydrogenated in acetic acid (40 ml.) in the presence of 10% palladised carbon (0·2 g.) at an initial hydrogen pressure of 60 lb./sq. in. The *product* (1·5 g., 80%) had b. p. 128—130°/0·1 mm. (Found: C, 82·8; H, 9·5; O, 7·6. $C_{15}H_{20}O$ requires C, 83·2; H, 9·3; O, 7·4%).

3-*Methoxyphenanthrene*.—The above material (VIIb) (0·75 g.) was dehydrogenated with 30% palladised carbon (0·08 g.) at 300° for 45 min. Chloroform-extraction, filtration, and evaporation gave 3-methoxyphenanthrene, m. p. 61° (picrate, m. p. 124°) (lit.,[11] m. p. 61° and 123—124°, respectively).

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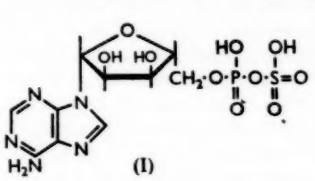
[10] Cf. Gates and Tschudi, *J. Amer. Chem. Soc.*, 1956, **78**, 1380.
[11] Pschorr, Wolfes, and Buckow, *Ber.*, 1900, **33**, 162.

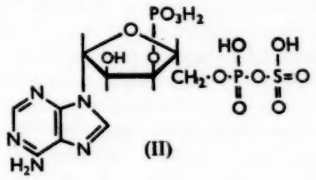
343. *Synthesis of "Active Sulphate" (Adenosine 3′-Phosphate 5′-Sulphatophosphate).*

By J. Baddiley, J. G. Buchanan, R. Letters, and A. R. Sanderson.

The pyridine–sulphur trioxide complex reacts with adenosine-3′ : 5′ diphosphate (III) in sodium hydrogen carbonate solution to give a mixture containing the cyclic phosphate (IV) and adenosine 3′-phosphate 5′-sulphatophosphate (II). The sulphatophosphate was indistinguishable, both chemically and enzymically, from "active sulphate."

The biosynthesis of sulphuric esters occurs, at least in a number of cases examined so far, by a sequence of enzymic reactions during which inorganic sulphate is converted into a sulphuric–phosphoric anhydride known as "active sulphate." These reactions have been studied by Lipmann and his collaborators,[1,2] and by Wilson and Bandurski[3] who have shown that adenosine triphosphate (ATP) reacts first with sulphate to give adenosine-5′ sulphatophosphate (I) (APS) which is then phosphorylated at the 3′-position by a second mol. of ATP to give adenosine 3′-phosphate 5′-sulphatophosphate (II) (active sulphate, PAPS). This intermediate is able to transfer its sulphate group to a variety of substrates in the presence of the appropriate enzyme.


(I)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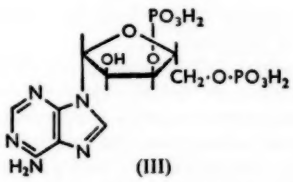
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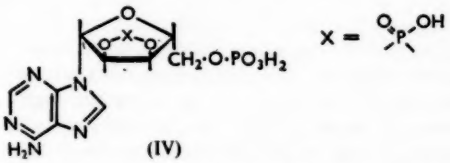
(IV)

The sulphatophosphate (I) was synthesised in these Laboratories[4] by reaction between adenosine-5′ phosphate and the pyridine–sulphur trioxide complex in sodium hydrogen carbonate solution, and independently by Reichard and Ringertz[5] who condensed inorganic sulphate with adenosine-5′ phosphate in the presence of di*cyclo*hexylcarbodiimide. An advantage of the former method lies in the ease of separation of the product. This synthesis was of much value in making available authentic adenosine-5′ sulphatophosphate required for the elucidation of the enzymic reaction sequences.[2,3]

A synthesis of active sulphate itself would require either the phosphorylation of adenosine-5′ sulphatophosphate or the sulphation of the 3′ : 5′-diphosphate (III) of adenosine. Whereas the latter method seemed promising, the necessary diphosphate (III) was not readily available when this work was started. It had been obtained by enzymic degradation of coenzyme A,[6] and more recently it has been identified as a co-factor in certain sulphate transfer reactions.[7] Preliminary experiments on the synthesis of "active

[1] Hilz and Lipmann, *Proc. Nat. Acad. Sci., U.S.A.*, 1955, **41**, 880.
[2] Robbins and Lipmann, *J. Biol. Chem.*, 1957, **229**, 837; 1958, **233**, 681, 686.
[3] Wilson and Bandurski, *Arch. Biochem. Biophys.*, 1956, **62**, 503; *J. Biol. Chem.*, 1958, **233**, 975.
[4] Baddiley, Buchanan, and Letters, *J.*, 1957, 1067.
[5] Reichard and Ringertz, *J. Amer. Chem. Soc.*, 1957, **79**, 2025.
[6] Wang, Shuster, and Kaplan, *J. Biol. Chem.*, 1954, **206**, 299.
[7] Gregory and Lipmann, *ibid.*, 1957, **229**, 1081.

sulphate" were carried out on a small sample of the diphosphate obtained by Dr. J. D. Gregory from natural sources. Larger quantities of a mixture of adenosine-2′ : 5′ and -3′ : 5′ diphosphate were prepared by direct phosphorylation of adenosine,[8] and exploratory synthetical experiments were carried out with this mixture. For a synthesis of active sulphate it was desirable to separate these isomers before sulphation, in view of the difficulties expected in separating the mixture of sulphatophosphates and other products which would be formed in the reaction with pyridine–sulphur trioxide. The 2′ : 5′- and 3′ : 5′-diphosphate were separated by ion-exchange chromatography;[9] pure 3′ : 5′-diphosphate obtained in this way was used in the present work.

Adenosine-3′ : 5′ diphosphate was treated with pyridine–sulphur trioxide in sodium hydrogen carbonate solution under conditions similar to those used in the synthesis of the sulphatophosphate (I). Paper chromatography and electrophoresis of the reaction mixture demonstrated the presence of several nucleotides. The principal components of this mixture were unchanged diphosphate and two new nucleotides. Both had higher R_P values than the diphosphate in the *n*-propyl alcohol–ammonia solvent but only one contained sulphate, as was indicated by acid-hydrolysis *in situ* followed by the barium–rhodizonic acid spray.*

The sulphur-free product was identified as adenosine 2′ : 3′-phosphate 5′-phosphate (IV) by its behaviour on paper chromatography and electrophoresis, and by acid- or alkali-hydrolysis to a mixture of adenosine-2′ : 5′ and -3′ : 5′ diphosphate. The formation of this cyclic phosphate is readily explained on the assumption that an initial reaction product was adenosine 5′-phosphate 3′-sulphatophosphate. Such a mixed anhydride would be unstable, decomposing spontaneously to inorganic sulphate and a 2′ : 3′-cyclic phosphate. In support of this it was shown that a mixture of adenosine-2′ and -3′ phosphate was converted in part into the 2′ : 3′-cyclic phosphate of adenosine by reaction with the pyridine–sulphur trioxide reagent in sodium hydrogen carbonate solution.[4] This ready cyclisation of mixed anhydrides at the 2′- or 3′-position in a nucleoside is also observed in the action of trifluoroacetic anhydride on nucleotides, where intermediate trifluoroacetic–phosphoric anhydrides are believed to be formed.[10]

The sulphur-containing nucleotide obtained in the above reaction was identified as "active sulphate" by comparison with authentic material. It had the same R_P value in several solvents and a characteristically high rate of migration on paper electrophoresis in a citrate buffer at pH 5·8. It was isolated by charcoal adsorption and ion-exchange chromatography under conditions similar to those used by Brunngraber [11] for its isolation from natural sources. The final product contained a trace of adenosine-3′ : 5 diphosphate, possibly arising through the known great acid-lability of the sulphatophosphate. The absence of phosphate migration during synthesis and isolation was demonstrated by alkali-hydrolysis of the product to adenosine-3′ : 5′ diphosphate and inorganic sulphate No 2′ : 5′-diphosphate was detected in the hydrolysate.

Enzymic assay of the synthetic material was carried out by Dr. J. D. Gregory in Dr. Lipmann's laboratory at the Rockefeller Institute. Difficulty was experienced through the partial decomposition of samples of the lithium salt during transit between this country and America. This was indicated by the low activity of these samples in the enzymic transfer of sulphate to *m*-aminophenol. The occurrence of considerable decomposition was confirmed by paper electrophoresis of material before dispatch and after receipt. A solution of the lithium salt containing a trace of ammonia was more stable. Special precautions were observed during the direct transport of this preparation by air between Newcastle and New York, and material examined by Dr. Gregory had a purity of 75—76%.

* A preliminary account of this work has been given (Baddiley, Buchanan, and Letters, *Proc. Chem. Soc.*, 1957, 147).

[8] Cramer, Kenner, Hughes, and Todd, *J.*, 1957, 3297.
[9] Baddiley, Buchanan, and Letters, *J.*, 1958, 1000
[10] Brown, Magrath, and Todd, *J.*, 1952, 2708.
[11] Brunngraber, *J. Biol. Chem.*, 1958, **233**, 472.

The activity of this preparation in the enzyme test was about 67% of what would be expected from chromatographic data. This rather low value is understandable, since the enzyme system used gives low values with active sulphate.

The experimental conditions for this synthesis were chosen in order to minimise the possible introduction of more than one sulphate group into the nucleotide. If both phosphate groups in adenosine-3′ : 5′ diphosphate were to react with the pyridine–sulphur trioxide reagent, the resulting di(sulphatophosphate) would decompose spontaneously to give adenosine 2′ : 3′-phosphate 5′-sulphatophosphate. Only traces of a compound with the paper-chromatographic properties expected for this cyclic phosphate were detected in the reaction mixture. This product increased in amount when a larger excess of sulphation reagent was employed, but it was not studied further.

Experimental

Adenosine-3′ : 5′ Diphosphate.—The nucleotide was separated from its 2′ : 5′-isomer by concave gradient elution chromatography on Dowex-1 (×2) resin (chloride form; 200—400 mesh), with calcium chloride and hydrochloric acid as eluting agents.[9] The eluate was adjusted to pH 7 with calcium hydroxide solution, then passed through a column of Dowex-50 (lithium form) resin. The product was isolated by freeze-drying, then extracting lithium chloride from the residue with acetone–ethanol (4 : 1) (4 × 100 c.c.). The *lithium salt* of adenosine-3′ : 5′ diphosphate had $\lambda_{max.}$ 256·5 mμ (ε 15,600) and $\lambda_{min.}$ 228 mμ (ε 3000) (Found: C, 25·0; H, 3·9; P, 12·7. $C_{10}H_{13}O_{10}N_5P_2Li_4,2H_2O$ requires C, 24·6; H, 3·5; P, 12·7%).

Adenosine 3′-Phosphate 5′-Sulphatophosphate.—Preliminary experiments were carried out on a micro-scale to determine the optimal conditions of synthesis. Products were separated by chromatography in solvent system *A* (see below), and estimated by elution from the paper and measurement of the optical density of the resulting solution at 257·5 mμ. Provided that adenosine 3′-phosphate 5′-sulphatophosphate has an extinction coefficient at 257·5 mμ typical of an adenosine-3′ : 5 diphosphate derivative, the maximum yield was 12%, under the conditions subsequently described.

The pyridine–sulphur trioxide complex (800 mg.) was added, with stirring, to a solution of the lithium salt of adenosine-3′ : 5′ diphosphate (200 mg.) and sodium hydrogen carbonate (1·2 g.) in water (12 c.c.) at 45°. After 40 min. at this temperature, the solution was cooled, diluted with iced water (500 c.c.), adjusted to pH 6 with N-formic acid, and passed through a column (7 × 5 cm.) of Norit A charcoal–Supercel silica (4 : 3), at a rate of 4 c.c./min. The charcoal had previously been washed with N-hydrochloric acid, N-ammonia, water, ethanol, and ether, then dried at 110° for 16 hr. The column was washed with water until the washings were free from sulphate and their optical density at 257·5 mμ was less than 0·1.

Nucleotides were eluted (1·5 c.c./min.) from the column with 50% aqueous ethanol which contained 1% of N-ammonia. The optical density (257·5 mμ) of the eluate indicated a recovery of 87%. The eluate was then passed through a column (7 × 4 cm.) of Dowex-1 (×2) resin (chloride form; 200—400 mesh), which was washed with water (3 l.). Concave gradient elution was performed using 2N-lithium chloride solution (2 l.) as eluant in the reservoir, and water (3 l.) in the mixing flask. Fractions (25 c.c.) were collected at a rate of 10 c.c./min., and the optical density at 260 mμ of each fraction was measured. Two sharp peaks were observed, the first between fractions 38 and 60, and the second between fractions 79 and 120. The former corresponded to adenosine-3′ : 5′ diphosphate, probably containing a trace of adenosine 2′ : 3′-phosphate 5′-phosphate (IV), while the latter corresponded to adenosine 3′-phosphate 5′-sulphatophosphate. The yield of sulphatophosphate, calculated from ultraviolet measurements, was about 10%. The fraction containing the desired nucleotide was passed through a charcoal–Supercel column (2 × 5 cm.), similar to that mentioned previously, at a rate of 10 c.c./min. After being washed with water (2 l.), the nucleotides were eluted with 50% aqueous ethanol (300 c.c.) which contained 1% of N-ammonia. The optical density of the eluate at 257·5 mμ indicated a recovery of 88%. The eluate was concentrated under reduced pressure below 35° and passed through a column (1 × 1 cm.) of Dowex-50 (×8) resin (lithium form; 200—400 mesh). Evaporation of the eluate and washings yielded a light-brown solid (19 mg.). A sample (5 mg.) of the lithium salt was chromatographed on paper in solvent *A*. The appropriate ultraviolet-absorbing area was eluted from the paper. [The ratios

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adenosine : P : ribose : S : N (total) : N (ammonium) were 1·00 : 2·02 : 0·96 : 0·96 : 8·95 : 3·95. The calculated ratios for the tetra-ammonium salt ($C_{10}H_{27}O_{13}N_9P_2S$) are 1 : 2 : 1 : 1 : 9 : 4.] Adenosine was determined spectroscopically, phosphorus by Allen's method [12] ribose by Mejbaum's method,[13] sulphur as inorganic sulphate after hydrolysis,[14] and the two forms of nitrogen by Johnson's method.[15]

A sample of the product was almost homogeneous when examined by paper chromatography and paper electrophoresis; about 5% of adenosine-3′ : 5′ diphosphate was present. The diphosphate content slowly increased on storage.

Hydrolysis with Alkali.—Adenosine 3′-phosphate 5′-sulphatophosphate (lithium salt; 1 mg.) was heated at 100° in 0·1N-sodium hydroxide, and the products were examined by paper chromatography in solvent *A*, after the removal of metal ions with Dowex-50 (ammonium form) resin. Hydrolysis was incomplete even after 2 hr. A sample of the resulting diphosphate was isolated by elution from the paper and, after evaporation of eluant, was re-chromatographed in solvent *B*. The diphosphate had the same R_P value as adenosine-3′ : 5′ diphosphate, no trace of the 2′ : 5′-isomer being observed.

Adenosine 2′ : 3′-Phosphate 5′-Phosphate.—The nucleotide with R_P 0·23 (solvent *A*), prepared in a small-scale sulphation experiment, was eluted from a paper chromatogram. It was homogeneous when examined on paper in M-ammonium acetate (pH 7·5)–ethyl alcohol (30 : 75) and *iso*butyric acid–0·5N-ammonia (10 : 6), in which it had R_P 0·2 and 0·34 respectively. When kept overnight at pH 12 and room temperature, it was converted into a mixture of the 2′ : 5′- and 3′ : 5′-diphosphates of adenosine.

Paper Chromatography.—Chromatography was carried out on Whatman No. 4 paper, which had previously been washed with dilute acetic acid and water. The following solvent systems were used: *A*, *n*-propyl alcohol–ammonia (*d* 0·88)–water (6 : 3 : 1). *B*, Saturated ammonium sulphate–0·1M-ammonium acetate–*iso*propyl alcohol (79 : 19 : 2).[16] Nucleotides were located by inspection under ultraviolet light (see Table).

	R_P in solvent	
	A	*B*
Adenosine-5′ phosphate	0·28	0·36
Adenosine-2′ phosphate	0·33	0·31
Adenosine-3′ phosphate	0·33	0·21
Adenosine-2′ : 5′ diphosphate ...	0·10	0·48
Adenosine-3′ : 5′ diphosphate ...	0·11	0·40
Adenosine-5′ pyrophosphate ...	0·10	0·50
Adenosine-5′ triphosphate	0·17	—
Adenosine 2′ : 3′-phosphate 5′-phosphate	0·23	—
Adenosine 3′-phosphate 5′-sulphatophosphate	0·18	0·29

Paper Electrophoresis.—Electrophoresis was carried out for 6 hr. on Whatman No. 1 paper soaked in 0·025M-sodium citrate buffer at pH 5·8, with a voltage gradient of 10 v per cm. (see Table).

	Distance moved towards anode (cm.)
Adenosine-5′ phosphate	18·7
Adenosine-2′ phosphate	20·2
Adenosine-3′ phosphate	20·2
Adenosine-2′ : 5 diphosphate	34·0
Adenosine-3′ : 5′ diphosphate	34·1
Adenosine-5′ pyrophosphate	29·6
Adenosine-5′ triphosphate ...	37·4
Adenosine 3′-phosphate 5′-sulphatophosphate	44·1

We thank Drs. J. D. Gregory and F. Lipmann for their helpful co-operation in carrying out the enzyme tests, and B.K.S. Air Transport for special facilities in connection with the transport of samples. This work was carried out during the tenure of Earl Grey and Salters Fellowships (by R. L. and A. R. S. respectively).

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[*Received, December 16th*, 1958.]

[12] Allen, *Biochem. J.*, 1940, **34**, 858.
[13] Mejbaum, *Z. physiol. Chem.*, 1939, **258**, 117.
[14] Iwasaki, Utsumi, Hagino, Tarutani, and Ozawa, *Bull. Soc. Chem. Japan*, 1957, **30**, 847.
[15] Johnson, *J. Biol. Chem.*, 1941, **137**, 575.
[16] Markham and Smith, *Biochem. J.*, 1951, **49**, 401.

344. *Dielectric Properties and Electrical Conductivity of Some Fused Metal Carboxylates.*

By P. G. T. Fogg and R. C. Pink.

Dielectric data and derived electrical conductivites are reported for a series of molten metal carboxylates. In fused zinc carboxylates and lead stearate the measured loss is due solely to direct-current conductivity but in magnesium and copper oleates relaxation effects are imposed on the direct-current conduction loss. In the melts the electrical conductivity increases exponentially with temperature. The very low conductivities of the melts may be explained on the assumption that fusion incompletely destroys the crystal lattice and that the charge carriers are aggregates bearing a limited number of charges in proportion to their mass. A contribution to the conductivity may also be made by simple unassociated ions but the proportion of these ions in the melts must be very small.

Although some of the properties of long-chain metal carboxylates, *e.g.*, their solubility in non-polar solvents and their low melting points,[1] suggest that they are essentially covalent compounds, measurements of dipole monents [2] and electrical conductivity in non-polar solvents [3] indicate that some of them are ionic. We have now investigated the dielectric properties and electrical conductivity of a series of bivalent metal carboxylates both in the molten and in the solid state, in order to provide experimental evidence on this point. No previous investigation of the electrical properties of these compounds in the molten state has been reported.

Experimental

Materials.—The metal carboxylates chosen were magnesium, zinc, and copper oleate, zinc laurate and decanoate, and lead stearate. They were prepared and purified as described elsewhere.[3]

Apparatus.—Dielectric-constant and dielectric-loss measurements were made in the frequency range 30 c./sec. to 300 kc./sec. with a capacitance bridge (General Radio Type 716-c) in conjunction with a resistance–inductance-bridge type oscillator and a stabilised high-gain wide-band amplifier and cathode-ray oscilloscope as indicator. The dielectric cell consisted of two partially silvered concentric Pyrex cylinders closed at the bottom and sealed at the top with a B24 joint. The air capacity of this cell was ~25 pF and its loss angle (tan δ) at 60 c./sec. was $>0{\cdot}001$. Its volume was about 3 ml. Finely powdered samples of the carboxylates were melted into it under dry oxygen-free nitrogen and before the electrical measurements were made bubbles of gas were removed by careful pumping. Under these conditions an analytical check indicated negligible decomposition of the samples during the period required by the measurements. The temperature of the cell was controlled to $\pm 0{\cdot}2°$ in an electrically heated aluminium block thermostat.

Dielectric Loss.—The dependence of dielectric loss factor ε'' on frequency for fused zinc laurate, decanoate, and oleate and lead stearate at the temperatures indicated is shown in Fig. 1. Where the whole of the loss in a dielectric is due to direct-current conduction it can be shown from a consideration of the voltage–current vectors that the dielectric-loss factor is inversely proportional to frequency, and the specific conductance σ can then be calculated from eqn. (1) where f = frequency in cycles per second. It is clear from Fig. 1. that this condition

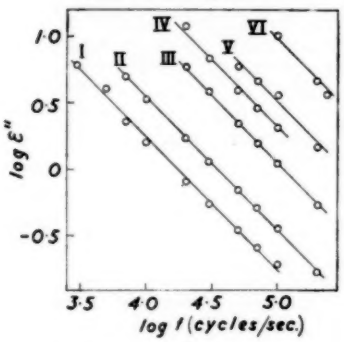
$$\sigma = 5{\cdot}5 \times 10^{-13}\, \varepsilon'' f \ (\text{ohm}^{-1}\ \text{cm.}^{-1}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

is met in the case of the fused zinc carboxylates and lead stearate and that in these cases the whole of the measured loss in this frequency range is due to direct-current conductivity. With copper oleate, however, inverse proportionality between loss factor and frequency was found

[1] Koenig, *J. Amer. Chem. Soc.*, 1914, **36**, 951.
[2] Banerjee and Palit, *J. Indian Chem. Soc.*, 1950, **27**, 385.
[3] Nelson and Pink, *J.*, 1954, 4412.

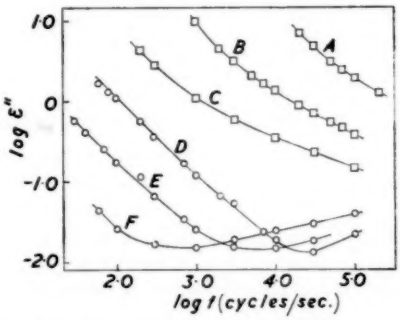
only at lower frequencies, and with magnesium oleate the results departed from a conductivity plot over the whole range (Fig. 2). Since fused magnesium oleate is exceptionally viscous, the departure from a conductivity plot indicated in Fig. 2 may possibly be explained on the basis of restricted movements of ions in a viscous medium.[4] It is possible that the dielectric absorption observed in copper oleate at higher frequencies is associated with a molecular orientation process but if this is so it is surprising that evidence of absorption at these frequencies was not obtained in the other carboxylates. Dielectric absorption in this frequency range, observed in

FIG. 1. *Effect of frequency on loss factor of molten carboxylates.*



(I) Zinc oleate (73°)
(II) ,, (93·5°)
(III) ,, (133°)
(IV) Zinc laurate (127°)
(V) Lead stearate (113·5°)
(VI) Zinc decanoate (131·5°)

FIG. 2. *Effect of frequency on loss factor of molten carboxylates.*



□ Magnesium oleate: *A* 185·5°, *B* 155°, *C* 135°.
○ Copper oleate: *D* 122·5°, *E* 93°, *F* 63°.

long-chain alcohols, has been attributed by Dalbert, Magat, and Surdut to the duration of life of molecular aggregates but it is not clear from their discussion how this could lead to dielectric loss.[5]

Electrical Conductivity.—Specific conductivities calculated from eqn. (1) are shown in the Table together with data for some other fused salts.[6,7]

Compound	Temp. range	σ (ohm^{-1} cm.$^{-1}$)	$E\sigma$ (kcal./mole)	A
Zinc decanoate	131·5—154°	$5{\cdot}56 \times 10^{-7}$—$1{\cdot}04 \times 10^{-6}$	9·6	$8{\cdot}02 \times 10^{-2}$
,, laurate	127—151	$1{\cdot}15 \times 10^{-7}$—$2{\cdot}57 \times 10^{-7}$	11·4	$1{\cdot}71 \times 10^{-1}$
,, oleate	73—133	$9{\cdot}3 \times 10^{-9}$—$6{\cdot}03 \times 10^{-8}$	8·7	$2{\cdot}89 \times 10^{-3}$
Copper oleate	63—122·5	$1{\cdot}95 \times 10^{-10}$—$5{\cdot}89 \times 10^{-9}$	15·2	1·34
Lead stearate	105—115	$5{\cdot}52 \times 10^{-8}$—$2{\cdot}63 \times 10^{-7}$	—	—
$KHSO_4$ [6]	211·8—300·5	0·049—0·141	6·2	33
$NaHSO_4$ [6]	190·0—310·2	0·079—0·256	5·7	38
KCl [7]	768	2·12	2·3	6·5
AgCl	600	4·48	—	—

Effect of Temperature.—The effect of temperature on the conductivity is shown in Figs. 3 and 4 (cooling curves). With the possible exception of lead stearate, a simple exponential relation was found in every case between conductivity and temperature. The high apparent dielectric constant of lead stearate prevented accurate loss measurements except over a limited temperature range. A feature of the result in the case of the zinc carboxylates was the time-lag in the establishment of equilibrium conditions when the temperature of the sample was changed.

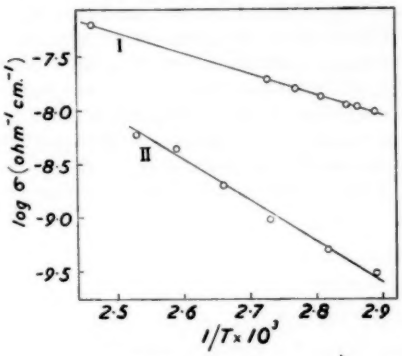
[4] Whitehead and Marvin, *Trans. Amer. Inst. Elect. Engrs.*, 1929, **48**, 313; Gemant, *Trans. Faraday Soc.*, 1935, **31**, 1582.
[5] Dalbert, Magat, and Surdut, "Polarisation de la Matière," Colloques Internationaux, Paris, 1949, 14.
[6] Rogers and Ubbelohde, *Trans. Faraday Soc.*, 1950, **46**, 1051.
[7] Biltz and Klemm, *Z. anorg. Chem.*, 1926, **152**, 267.

Apparent activation energies for conduction E_σ and values of A calculated from the equation (2) are also shown.

$$\sigma = A \exp(-E\sigma/RT) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

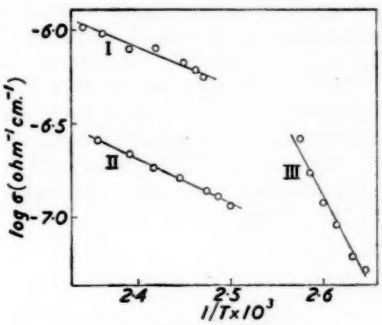
Dielectric Constant.—In all the carboxylates the apparent dielectric constant of the melt increased very rapidly at low frequencies. The behaviour of fused zinc laurate which was typical of the group is shown in Fig. 5 which also gives results for the solid phase at several temperatures. There is a sharp fall in dielectric constant when solidification takes place. At

FIG. 3. *Effect of temperature on conductivity.*



(I) Zinc oleate
(II) Copper oleate.

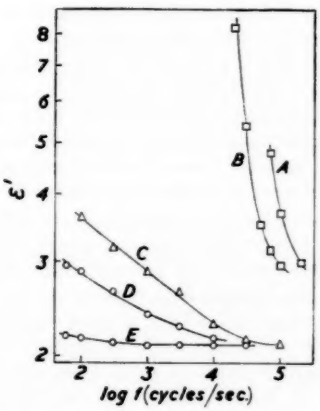
FIG. 4. *Effect of temperature on conductivity.*



(I) Zinc decanoate.
(II) Zinc laurate.
(III) Lead stearate.

FIG. 5. *Effect of frequency on dielectric constant.*

⊡ Molten zinc laurate: *A* 151°, *B* 129°.
△ Solid zinc laurate immediately after solidification: *C* 120°.
⊙ Solid zinc laurate after storage for 18 hours: *D* 121°, *E* 109·5°.



high frequencies the value for the solids tended to a value between 2 and 3. Just below the m. p. the dielectric constant at low frequencies immediately after solidification was found to be considerably greater than the value after the solid had been stored overnight at the same temperature (Fig. 5). This decrease may be due to a gradual increase in ordering in the lattice with time. A very similar effect has been reported in other long-chain compounds by Meakins and Mulley.[9]

In view of the relatively high conductivity of the melt the sharp rise in apparent dielectric constant observed in the melt as the frequency falls may be accounted for largely by electrode polarisation or possibly by the development of a space charge in the neighbourhood of the electrode surfaces. If ionic micelles are present in these systems their discharge at the electrodes

[8] Lowry, *Phil. Mag.*, 1928, **5**, 1072.
[9] Meakins and Mulley, *Austral. J. Sci. Research*, 1951, *A*, **4**, 365.

may present considerable steric difficulties since it may be assumed that the electrical charge will be located inside a micelle and be surrounded effectively by an insulating layer of hydrocarbon chains. Johnston and Cole [10] found that the apparent dielectric constant of liquid formic acid which has a specific conductance at 25° of 6×10^{-5} ohm^{-1} cm.$^{-1}$ did not differ from ε at 10 kc./sec. but was approximately ten times as great at 20 c./sec. They showed that this apparent large increase could be accounted for satisfactorily by the combined effects of direct current conduction and electrode polarisation.

Discussion

The most interesting property of the molten carboxylates is their low conductivity in comparison with most other fused salt systems which have conductances greater by a factor of at least 10^6. On the other hand the measured conductivities differ by a large factor from those of non-ionic liquids, indicating the presence in the melts of ions or charged aggregates. In view of the well-known tendency of this group of compounds to form aggregates in non-polar solvents, the simplest explanation is that fusion incompletely destroys an ionic crystal lattice and that some of the resultant aggregates or micelles carry a resultant electric charge. Ionisation processes in the system could then be represented by the equilibria (M = metal; A = acid radical):

$$MA_2 \rightleftharpoons MA^+ + A^-$$
$$(MA_2)_n + MA^+ \rightleftharpoons (MA_2)_nMA^+$$
$$(MA_2)_n + A^- \rightleftharpoons (MA_2)_nA^-$$

where MA_2 could be a neutral molecule or an ionic doublet. The low mobility of charge carriers of the micelle type would account for their small contribution to the conductivity. This type of aggregate is similar to that which is believed to be responsible for conduction in solutions of metal carboxylates in non-polar solvents.[3] The presence of micelles in these melts is supported qualitatively by their high viscosity. Lawrence [11] also has concluded, from a study of their melting characteristics, that many metal soaps pass through a viscous stage in which the melt consists of large aggregates or micelles. The low conductivities of the melts are no doubt accounted for partly by this high viscosity.

A contribution to the total conductivity may also be made by the kinetically free simple ions MA^+ and A^- although the low measured conductivities indicate that the proportion of these present must be very small. The only comparable data are for the alkylammonium picrates,[12] which have specific conductivities of the order of 10^{-2} ohm^{-1} cm.$^{-1}$. These relatively low conductivities have been interpreted by Greenwood and Martin [13] as implying limited dissociation, the average value of α, the degree of ionic dissociation, for a series of primary alkylammonium picrates being estimated as 36%. These authors distinguish between ionisation which implies separation of charge within the molecule and ionic dissociation which involves the separation of a molecule into anions and cations which are free to migrate under an applied potential.

Effect of Temperature.—For non-associated ionic melts like the alkali halides [7] an exponential relation (2) has been found between electrical conductivity and temperature.

For associated melts, on the other hand, Rogers and Ubbelohde [6] have pointed out that a different relation (3) should hold, where B' and B are constants and b is a constant related

$$\ln \sigma = B - (B'/T) \exp (b/T) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

to the activation energy involved in the dissociation. A similar relation would hold if simple ions were the charge carriers in a partly ionised non-associated melt and the ionisation was temperature-dependent. Since a simple exponential relation was found in every

[10] Johnston and Cole, *J. Amer. Chem. Soc.*, 1951, **73**, 4536.
[11] Lawrence, *Trans. Faraday Soc.*, 1938, **34**, 660.
[12] Walden, Ulich, and Birr, *Z. phys. Chem.*, 1927, **130**, 495; 1928, **131**, 1, 21.
[13] Greenwood and Martin, *J.*, 1953, 1431.

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case between conductivity and temperature (Figs. 3 and 4) the present results appear to indicate that the carboxylate melts are simple non-associated liquids. A very similar anomaly was observed by Rogers and Ubbelohde [6] in the case of the alkali hydrogen sulphate melts which on the basis of viscosity measurements and on other grounds clearly contained chain-like aggregates linked by hydrogen bonds, and yet obeyed equation (2) within the limits of experimental error. If ionic micelles are actually responsible for the conductivity in the carboxylate melts the fact that equation (2) is obeyed may mean that over the temperature range of these experiments there is no redistribution of the micelles leading to a substantial change in the number of current carriers or that the redistribution of micelle size is such a slow process that only the change in conductivity due to decreased mobility is detected on lowering the temperature. Alternatively, the bulk of the current in these melts may be carried by the simple ions MA^+ and A^-. Against the latter view is the magnitude of the E values found in these experiments which is much higher than in non-associated melts like the alkali halides and approximates more closely to the values found in the associated bisulphate melts. Unfortunately the paucity of data on the electrical properties of melts precludes further comparison.

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345. *The Water-soluble Polysaccharides of* Cladophora rupestris. *Part II.*[1] *Barry Degradation and Methylation of the Degraded Polysaccharide.*

By J. J. O'DONNELL and ELIZABETH PERCIVAL.

Repeated successive treatment of the water-soluble polysaccharide, cladophoran, with periodate and with phenylhydrazine gave a 25% yield of a degraded polymer containing L-arabinose, D-galactose, and L-rhamnose and 15% of sulphate groups. Evidence is presented that sulphate groups are linked to sugar residues other than galactose. Methylation studies established the linkages present in the degraded material. The significance of these results in relation to the whole polymer is discussed.

THE water-soluble extract from the green seaweed, *Cladophora rupestris*, is a heteropolysaccharide material, which failed to separate into simple polymers when subjected to the usual fractionation techniques. The presence of 20% of organically bound sulphate made complete methylation difficult. However, separation and characterisation of a number of the sugars in the hydrolysate of the methylated material revealed some of the linkages present in the original polysaccharide, although it was not possible to advance any general structure for the polysaccharide or to allocate the sulphate residues to any particular sugar.[1]

Repeated degradation by Barry's method [2] appeared to offer a means of obtaining information on the structure of the inner part of this molecule. A single Barry degradation involves oxidation of the polysaccharide with periodate, followed by treatment of the oxo-polysaccharide with phenylhydrazine. This treatment removes all the residues in the original molecule which contained α-glycol groups and new vicinal hydroxyl groups are exposed in the degraded polymer. The process can then be repeated, and in this way successive layers of residues are removed from the periphery of the molecule. In the present experiments the reduction of periodate and the production of formic acid were measured for each oxidation. At the same time the oxo- and degraded polymers were

[1] Part I, Fisher and Percival, *J.*, 1957, 2666.
[2] Barry and McCormick, *J.*, 1957, 2777; Finan and O'Colla, *Chem. and Ind.*, 1958, 493, 1404.

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isolated at each stage and their constituent sugars and sulphate and nitrogen contents were determined (see Tables 1 and 2).

TABLE 1.

	IO_4 reduced (moles/kg.)	Formic acid (moles/kg.)	Yield g.	Yield % †	N (%)
O_1 *	2·82	1·8	18·2	89	—
O_1D_1	—	—	13·7	63	3·5
D_1O_2	1·97	0·9	9·9	80	2·7
O_2D_2	—	—	6·3	66	4·2
D_2O_3	2·52	1·0	4·8	73	2·4

* O and D refer to the respective oxo- and degraded polysaccharides isolated. The second letter indicates the nature of the last treatment and the subscripts correspond to the number of such treatments.

† In calculating percentage yields of oxo-polysaccharide, allowance is made for material consumed during measurements.

Analysis of the hydrolysate of the oxo-polysaccharide O_1 confirmed the cleavage of all the xylose and a considerable proportion of the galactose units. For these sugars to be attacked by periodate they must be present as end-group or linked only through positions 1 and 4 (and/or 6 in the case of galactose) in the original polysaccharide. Glyoxal bisphenylhydrazone was isolated from the ethereal extract of the degraded material O_1D_1. This is in keeping with the cleavage of 1 : 4-linked xylose and galactose residues. No

TABLE 2.

	Molar proportions of sugars [3]					Ash (%)	SO_4 (%)	N (%)
	Arabinose	Galactose	Glucose	Xylose	Rhamnose			
Cladophoran	4·0	3·0	0·23	1·1	0·5	15·7	18·3	1·7
O_1	4·0	0·88	0·35	—	0·67	14·9	19·2	1·5
O_1D_1 *	—	—	—	—	—	15·6	16·6	3·5
D_1O_2	4·0	0·89	—	—	0·65	12·3	17·5	2·7
O_2D_2 *	—	—	—	—	—	12·8	16·9	4·2
D_2O_3	1·0	1·04	—	—	0·56	13·4	15·2	2·4

* A sample hydrolysate of the degraded material was chromatographically indistinguishable from that of the oxo-polysaccharide (visual examination).

other phenylhydrazone fragments were detected in this extract, although the presence of a large amount of *N*-acetylphenylhydrazine may be responsible for the failure to detect glycerosazone which has very similar solubility and chromatographic properties.

The second oxidation consumed one mole of periodate for every three sugar residues. Apparently all the glucose residues (*ca.* 5% of the molecule) were attacked, since this sugar was absent from the hydrolysate of the oxo-polysaccharide D_1O_2. The relative proportions of the other sugars were unchanged, and they must therefore have been attacked to approximately the same extent in this second oxidation. The disappearance of glucose, which was verified by a second experiment, is difficult to understand. Earlier work on cladophoran had indicated that at least part of the glucose was present as a separate 1 : 3-linked glucan. This would be immune to periodate attack, except at the ends of the chains. It may be that the glucan is a small, highly branched molecule with other linkages also present and that two oxidations are necessary to remove the branches and leave a linear molecule of dialysable proportions.

During the third oxidation, a large proportion of the arabinose residues were attacked, and an oxo-polysaccharide D_2O_3 containing arabinose : galactose : rhamnose in the molar proportions of 1 : 1 : 0·56 and representing *ca.* 25% of the original material was isolated.

Degradation removes those units from the polymer that have previously been attacked by periodate. The calculated yields of O_1D_1 and of O_2D_2, based on this loss, are in good

[3] Pridham, *Analyt. Chem.*, 1956, **28**, 1967.

agreement with the actual yields of the respective degraded polymers (see Table 1). Although the nature of the nitrogen-containing groups in the degraded material is uncertain, they are apparently attacked by periodate since the nitrogen content is reduced on oxidation.

Complete methylation of the degraded polymer D_2O_3 was carried out by the method of Fear and Menzies.[4] After hydrolysis of the methylated material with hydrochloric acid, and neutralisation with silver carbonate, the mixture of neutral methylated sugars and inorganic salts was evaporated to dryness. Exhaustive extraction of the residue with water was efficacious in leaving brown nitrogenous material adsorbed on the precipitated silver salts. The neutral methylated sugars were separated on a cellulose column, and the remainder of the contaminating nitrogenous material was removed in the first fraction as a fast-flowing mixture which was discarded. 2 : 4-Di-*O*-methylrhamnose (1 part), 2 : 4-di-*O*-methylarabinose (4 parts), 2-*O*-methylarabinose (1 part), D-galactose (1 part), 2 : 4 : 6-tri-*O*-methylgalactose (3 parts), 6-*O*-methylgalactose (1 part) and L-rhamnose (3 parts) were separated and characterised. None of these sugars has methoxyl groups on adjacent carbon atoms. This is in keeping with the immunity of the material D_2O_3 to further attack by periodate. With the exception of the proportion of rhamnose, which is somewhat higher in the hydrolysate of the methylated material, the relative proportions of the methylated derivatives are in good agreement with those of the sugars in the degraded material D_2O_3 (Table 2).

Earlier studies [1] revealed the presence of galactofuranose residues in cladophoran. While it is recognised that the present experiments have not eliminated the possibility of the presence of arabo- and rhamno-furanose residues, the resistance of these units in the polysaccharide to mild acid-hydrolysis is in favour of a pyranose structure. Therefore, all the available evidence being borne in mind, the linkages which may be present in the centre of the cladophoran molecule are:

..3Rl..	...3Al..	..3Al.. 4	..3Gal.. 4 6	..3Rl.. 4	3Gal.. 4	..3Gal..
(1)	(4)	(1)	(1)	(3)	(1)	(3)

R = rhamnose, A = arabinose, Ga = galactose.

Comparison of these methylation results with those from the whole polymer show that the first four sugars given above are common to the hydrolysates of both methylated materials. Of the remaining derivatives isolated from the methylated degraded hydrolysate all except the L-rhamnose could have been formed, from lesser methylated derivatives present in the undegraded hydrolysate, by methylation of hydroxyl groups set free during the degradation. The failure to separate any free rhamnose from the hydrolysate of the methylated whole cladophoran is not very surprising when it is remembered that the total rhamnose content corresponded to *ca.* 5%, and that some seventeen different sugar derivatives were shown to be present in this hydrolysate including three different methylated rhamnoses.

The sulphate content of the various degraded products remained approximately constant, indicating that the sulphate ester groupings are spread relatively evenly throughout the molecule. The sulphate content of the degraded cladophoran D_2O_3 is equivalent to about one sulphate group per 3 or 4 sugar residues, and earlier work [1] has shown that this is not reduced on methylation. The 1 : 3-linked galactose is unlikely to be present as end group carrying sulphate on $C_{(3)}$, as such sulphate would be labile in the alkaline conditions of methylation and give rise to 3 : 6-anhydrogalactose.[5] If the sulphate groups are linked to galactose at all then, since they are not labile to alkali, they are probably located at position 4. Only one residue in seven of the sugars present in the hydrolysate of the methylated degraded material is a galactose unit with $O_{(4)}$ available for linkage.

[4] Fear and Menzies, *J.*, 1926, 937.
[5] Percival, *Quart. Rev.*, 1949, **3**, 369.

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At least some of the sulphate groups must therefore be carried by either arabinose and/or rhamnose. This is the first evidence of sulphate groups linked to residues other than galactose in seaweed polysaccharides. The large amount of quadruply linked rhamnose in the polymer makes this sugar a very likely site for these residues, but a definite answer to this question must await other methods of investigation.

Certain broad conclusions can be drawn from these experiments: the material has a highly branched structure, with xylose and galactose units at the ends of the branches, whereas galactose, arabinose, and rhamnose residues comprise the centre of the molecule. Sulphate groups are linked to residues both on the outer branches and in the centre of the molecule. Finally, after three oxidations and two treatments with phenylhydrazine the molecule is still sufficiently large to be retained by a dialysis sac.

Experimental

Paper partition chromatography was carried out on Whatman No. 1 filter paper. Paper ionophoresis [6] was done in borate buffer (pH 10) at 750 v for 5 hr. Evaporations were carried out at 40°/15 mm. Specific rotations were measured in water at 18°.

The water-soluble polysaccharide, cladophoran (26·3 g.), $[\alpha]_D$ +69° (ash, 13·7%), was alternately oxidised with periodate and degraded with phenylhydrazine three times. In a typical experiment the polysaccharide (4% concentration) was treated in the dark at room temperature with 0·1M-sodium metaperiodate and the course of the reaction followed by measuring the periodate reduced [7] and the formic acid released [8] on samples (1 c.c.) withdrawn at intervals (see Table 1). After 50 hr. the reaction had reached completion, and the excess of periodate was removed with sulphur dioxide and the mixture dialysed until free from inorganic ions. An aliquot part was removed and hydrolysed with N-sulphuric acid at 100° for 6 hr. The molar proportions of the sugars in the resulting syrup were determined by Pridham's method [3] (see Table 2). For this method of estimation a synthetic mixture of the sugars present in the hydrolysate was made by dissolving millimolar quantities of these sugars in 25 c.c. of water. Measured quantities of this mixture (0·02, 0·04, 0·06, 0·08 c.c.) were applied from an Agla microburette at intervals along the starting line of a paper chromatogram (20 × 40 cm.). Also spotted on the paper were samples of the hydrolysate. After elution the chromatogram was sprayed with a 1% solution of freshly prepared *p*-anisidine hydrochloride and heated at 130° for 10 min. Each of the coloured spots which developed, together with suitable blanks, were cut out and left for 10 min. in 3 c.c. of methanolic stannous chloride (1 g. of stannous chloride dissolved in 5 c.c. of water, 90 c.c. of methanol added, and the mixture filtered). The density of the resulting solution was then measured in a Unicam spectrophotometer at the wavelength of maximum absorbance for the particular sugar being examined. When the readings for the standard solutions of the respective sugars were plotted against concentration a straight-line graph was obtained in each case, and these were used to determine the unknown materials. A complete duplication of the experiment ensured accuracy within ±5%.

The oxo-polysaccharide in the remainder of the solution was isolated by freeze-drying. The second oxidation was not complete until after 70 hr. and the third oxidation after 86 hr.

The oxo-polysaccharide was degraded by heating a 4% aqueous solution at 100° for 2 hr. with 7% acetic acid and 3% phenylhydrazine. After exhaustive extraction with ether and dialysis the degraded polysaccharide was isolated, by freeze-drying, as a light yellow powder. Further extraction with ether failed to reduce the nitrogen content.

The ethereal extracts after evaporation to dryness and extraction with glacial acetic acid afforded a brown powder. Dissolution in ether and addition of light petroleum afforded yellow crystals of glyoxal bisphenylhydrazone (0·9 g.), m. p. and mixed m. p. 167°. Removal of the acetic acid yielded crystalline *N*-acetylphenylhydrazine, m. p. and mixed m. p. 124°.

Methylation of the Degraded Cladophoran D_2O_3.—Thallium hydroxide (6 g.) and an aqueous solution of cladophoran D_2O_3 (3·6 g.; 30 c.c.) were freeze-dried and the product was refluxed overnight with methyl iodide (25 c.c.).[4] After evaporation to dryness the residue was exhaustively extracted with methanol (3 × 25 c.c.), hot 50% aqueous methanol (3 × 25 c.c.),

[6] Foster, *Chem. and Ind.*, 1952, 1050.
[7] Fleury and Lange, *J. Pharm. Chim.*, 1933, **17**, 107.
[8] Chanda, Hirst, Jones, and Percival, *J.*, 1950, 1289.

and hot water (3 × 25 c.c.). The combined extracts were re-treated with thallium hydroxide and methyl iodide. After four methylations in all, the final residue was exhaustively extracted with chloroform. Removal of the chloroform from the combined extracts gave a brown powder (1·88 g.) (Found: OMe, 26·7%). Several methylations with Purdie reagents failed to raise the methoxyl content above 26·9%.

Hydrolysis of the Methylated Polysaccharide and Characterisation of the Methylated Sugars.— The above powder (1·80 g.) was hydrolysed under reflux with N-methanolic hydrogen chloride–water (9 : 1 by vol.) for 7 hr. Following neutralisation with silver carbonate and evaporation to dryness, the residue was thoroughly extracted with water. Removal of the water from the aqueous extracts and chloroform-extraction of the residue gave on evaporation an amorphous hydrolysate (0·96 g.). This was separated into its constituents on a cellulose column (55 × 2·3 cm.). After elution of five fractions with a water-saturated mixture of light petroleum (b. p. 60—80°)–butan-1-ol (8 : 2), the proportions were changed to 7 : 3. R_G values are recorded for paper chromatograms developed with butan-1-ol–ethanol–water (4 : 1 : 5). The products of demethylation [1] were detected by paper chromatography. The following fractions were collected:

Fraction 1, a yellow syrup (213 mg.) of R_G 1·05 (Found: N, 14·3%).

Fraction 2, syrupy 2 : 4-di-*O*-methylrhamnose (40 mg.), R_G 0·83, $[\alpha]_D$ −17° (*c* 0·3) (Found: OMe, 33·6. Calc. for $C_8H_{16}O_5$: OMe, 32·3%); demethylation gave only rhamnose; nucleation with an authentic specimen afforded needles of 2 : 4-di-*O*-methylrhamnose [9] with m. p. and mixed m. p. 82—83°.

Fraction 3, syrupy 2 : 4-di-*O*-methylarabinose (162 mg.), R_G 0·67, $[\alpha]_D$ +28° (*c* 2·0) (Found: OMe, 34·9. Calc. for $C_7H_{14}O_5$: OMe, 34·8%); demethylation of a portion of the syrup gave only arabinose; the derived anilide [10] had m. p. 126° and gave an *X*-ray powder photograph identical with that of 2 : 4-di-*O*-methyl-*N*-phenyl-L-arabinosylamine.

Fraction 4, syrupy 2 : 4 : 6-tri-*O*-methylgalactose (143 mg.), R_G 0·64, which crystallised from methanol; the crystals had m. p. 116°, $[\alpha]_D$ +88° (*c* 0·92) [11] (Found: OMe, 41·7. Calc. for $C_9H_{18}O_6$: OMe, 41·9%); demethylation gave only galactose.

Fraction 5, syrupy 2-*O*-methylarabinose (37 mg.), R_G 0·43, $[\alpha]_D$ +74° (Found: OMe, 18·0. Calc. for $C_6H_{12}O_5$: OMe, 17·8%); this was chromatographically and ionophoretically identical with authentic 2-*O*-methylarabinose and in keeping with this structure failed to give a red spot on spraying of a paper chromatogram with triphenyltetrazolium hydroxide; [12] the derived phenylhydrazone had m. p. 115°.

Fraction 6, crystalline L-rhamnose (89 mg.), R_G 0·30, $[\alpha]_D$ +8·2 (const.), m. p. and mixed m. p. 68°.

Fraction 7, syrupy 6-*O*-methylgalactose (23 mg.), R_G 0·23, $[\alpha]_D$ +74° (*c* 1·1) (Found: OMe, 15·1. Calc. for $C_7H_{14}O_6$: OMe, 16·0%); demethylation gave only galactose; the derived phenylhydrazone had m. p. 117°.[13]

Fraction 8, crystalline D-galactose (46 mg.), R_G 0·10, $[\alpha]_D$ +80° (const.), m. p. and mixed m. p. 162—164°.

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[9] Charalambous and Elizabeth Percival, *J.*, 1954, 2443.
[10] Andrews, Ball, and Jones, *J.*, 1953, 4090.
[11] Bell and Williamson, *J.*, 1938, 1196.
[12] Wallenfels, *Naturwiss.*, 1950, **37**, 491.
[13] Pacsu and Trister, *J. Amer. Chem. Soc.*, 1940, **62**, 2301.

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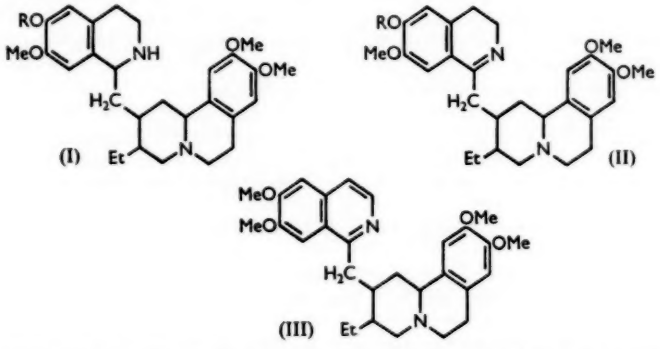
346. *Ipecacuanha Alkaloids. Part I. Fractionation Studies and the Isolation of Two New Alkaloids.*

By A. R. Battersby, G. C. Davidson, and B. J. T. Harper.

The alkaloids of ipecacuanha have been fractionated by countercurrent distribution. A simple method for the isolation of all previously known non-phenolic alkaloids has been developed and two new alkaloids (protoemetine and ipecac-alkaloid A) have been isolated. The infrared spectrum of *O*-methylpsychotrine has been compared with the spectra of model compounds; it is thereby confirmed that the double bond in this alkaloid is endocyclic.

It has been firmly established that ipecacuanha root contains four other bases in addition to emetine (I; R = Me), the major alkaloid. Paul and Cownley [1] isolated the phenolic alkaloids cephaeline (I; R = H) and psychotrine (II; R = H), to which Pyman [2] added the non-phenolic *O*-methylpsychotrine (II; R = Me) and emetamine (III). All were obtained by fractional crystallisation of the bases or of suitable salts. In addition, Hesse [3] claimed the isolation of two other alkaloids which he named ipecamine and hydroipecamine. Present knowledge of the alkaloids of ipecacuanha supports Pyman's view [2] that Hesse's products were mixtures.



When emetine is isolated from the total non-phenolic alkaloids of ipecacuanha, far more basic material (referred to as " mixed bases " below) remains in the mother-liquor than can be accounted for by the *O*-methylpsychotrine and emetamine present. Large quantities of these mixed bases are obtained as residues from the commercial extraction of emetine, a process which, fortunately for the present work, involves mild conditions throughout. Our interest in the biogenesis of alkaloids prompted us to fractionate these bases by countercurrent distribution with the aim of developing an improved method for the isolation of the known alkaloids and, more importantly, of detecting any new bases. This combination of a large-scale extraction with a powerful fractionation tool made it probable that biogenetic intermediates or substances derived from them, by chance methylation for example, could be isolated.

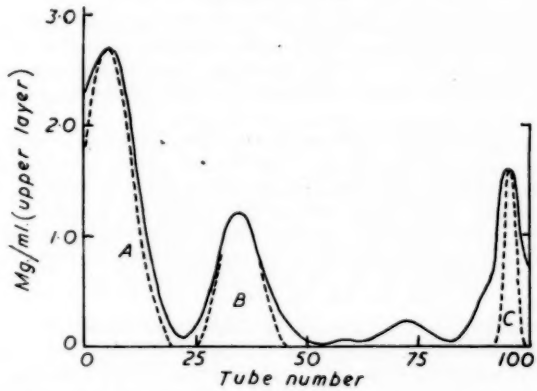
The result of distributing the mixed bases between ethyl acetate and aqueous phosphate buffer (pH 6·4) for 95 transfers is shown in the Figure. Material corresponding to peak *C* yielded emetamine (III) as its crystalline hydrogen oxalate. The width of this peak, compared with the calculated shape, shows clearly that emetamine is not the only weak base in ipecacuanha. *O*-Methylpsychotrine (II; R = Me) was isolated as the hydrogen

[1] Paul and Cownley, *Pharm. J.*, 1894, **25**, 111, 373, 690.
[2] Pyman, *J.*, 1917, **111**, 419; Brindley and Pyman, *J.*, 1927, 1067.
[3] Hesse, *Annalen*, 1914, **405**, 1.

oxalate from material represented by peak *B*, in quantity corresponding to 72% of the total base present, and that represented by peak *A* yielded emetine (I; R = Me) as its crystalline hydrobromide. Thus all the known non-phenolic alkaloids of ipecacuanha can be readily separated in a single distribution. The yield of emetine in different runs only accounted for 20—30% of the base in peak *A* and further investigation of this fraction is planned.

Our main effort was concentrated on the section between peaks *B* and *C* where there were signs of new alkaloids well separated from the known bases. In the large-scale work, a partial separation of the bases was first carried out in a distribution of seven transfers and the desired fraction, contaminated by some *O*-methylpsychotrine, was further fractionated to give a new alkaloid. This was very unstable as the free base and was rapidly destroyed in the presence of aqueous alkali. It did, however, form a stable crystalline perchlorate, $C_{19}H_{27}O_3N,HClO_4$. The yield of pure salt corresponded to 0·002% of the dry ipecacuanha root used for the original extraction. This alkaloid is named protoemetine and its structure is considered in the following paper.

Countercurrent distribution of the ipecacuanha alkaloids. The full curve represents the experimental results, and the broken curve the theoretical values.



A second new alkaloid was isolated from the bases which move rapidly in the distribution experiments. Until sufficient is known about its structure to allow an apt trivial name to be chosen, we designate this base ipecac-alkaloid A. It is crystalline and yields a crystalline oxalate and picrate. The yield as oxalate is only 5×10^{-4}% based upon dry ipecacuanha root so that sufficient quantities have not yet been available to allow its molecular formula to be established with certainty. However, some preliminary work, including analysis of salts, has been carried out. The ultraviolet spectrum of the alkaloid oxalate is characteristic of a veratrole residue and the Zeisel determination establishes the presence of alkoxyl groups. The infrared spectrum of the free base shows no absorption corresponding to >CO, OH or >NH; a band at 1643 cm.$^{-1}$ suggests unsaturation but the alkaloid oxalate was recovered unchanged after attempted mild hydrogenation over platinum. Further progress must await the isolation of greater quantities of this alkaloid.

With pure *O*-methylpsychotrine readily available to us from the fractionation studies, the opportunity has been taken to study further the position of the double bond in this alkaloid. Openshaw and Wood [4] found that the ultraviolet absorption of *O*-methylpsychotrine corresponds to the presence of a 3 : 4-dihydro*iso*quinoline residue. In support of this, the infrared spectrum of the alkaloid shows no absorption in the NH-stretching

[4] Openshaw and Wood, *J.*, 1952, 391.

region whereas emetine absorbs as expected at 3310 cm.$^{-1}$. Also, the former spectrum shows a triplet in the 1550—1650 cm.$^{-1}$ region (see Table). This triplet appears in all the model 3 : 4-dihydro*iso*quinolines examined, including one compound unsubstituted in the 1-position and in which the double bond must necessarily be endocyclic. Only one peak, or in one case a doublet, appears between 1550 and 1650 cm.$^{-1}$ in the spectra of 1 : 2 : 3 : 4-tetrahydro*iso*quinolines. Thus, the sum of the available evidence leaves no doubt that structure (II; R = Me) correctly represents *O*-methylpsychotrine.

Compound	$\nu_{max.}$* (1550—1650 cm.$^{-1}$)
3 : 4-Dihydro-6 : 7-dimethoxy-1-methyl*iso*quinoline	1630, 1607, 1575
1 : 2 : 3 : 4-Tetrahydro-6 : 7-dimethoxy-1-methyl*iso*quinoline	1608
1 : 3-Bis-(3 : 4-dihydro-6 : 7-dimethoxy-1-*iso*quinolyl)propane	1628, 1608, 1578
3-(3 : 4-Dimethoxyphenyl)-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline	1622, 1606, 1573
3-(3 : 4-Dimethoxyphenyl)-1 : 2 : 3 : 4-tetrahydro-6 : 7-dimethoxy*iso*quinoline	1610, 1595
1-*cyclo*Hexylmethyl-3 : 4-dihydro-6 : 7-dimethoxy*iso*quinoline[5]	1625, 1612, 1570
6-Benzyloxy-3 : 4-dihydro-7-methoxy*iso*quinoline [5]	1628, 1602, 1576
O-Methylpsychotrine	1618, 1610, 1576
Emetine	1610

* Determined in Nujol mulls with the exception of emetine, which was examined as a film.

Experimental

The small-scale countercurrent distributions (up to 10 g. of base) were carried out in a fully automatic glass machine [6] of 100-tubes (upper and lower phase volumes each 10 ml.) at 21° ± 2°. The tubes were numbered 0, 1, 2 . . . and the upper phase was transferred. Analyses were done by weight,[7] on the upper phase. Solutions in organic solvents were dried (Na_2SO_4) and evaporated at $\not>$40° under a reduced pressure of nitrogen.

Analytical samples were dried at 100° over phosphoric oxide *in vacuo* unless otherwise stated.

Small-scale Fractionation of Total Bases.—The mother-liquors from the isolation of emetine from ipecacuanha root (409 kg.) were made alkaline with aqueous ammonia and extracted four times with ethyl acetate. After being washed with water, the organic layers were dried and evaporated, to give a dark brown gum (400 g.). A portion (1·26 g.) was scattered over tubes 0—4 in the machine and then distributed for 95 transfers between ethyl acetate and aqueous buffer made from 0·5M-KH_2PO_4 (5 vol.) and 0·5M-K_2HPO_4 (3 vol.). Analysis showed three major peaks (Figure).

Large-scale Fractionation of Total Bases.—(a) *Isolation of* O-*methylpsychotrine.* The above mixed bases (200 g.) were fractionated in a 7-transfer countercurrent distribution in large bottles between ethyl acetate and the aqueous buffer used in the foregoing experiment. The phase volume was 3 l. and the *lower* layer was transferred. Bottles 2—5 were worked up for bases in the following way. The aqueous layer in each bottle was basified with ammonia and then shaken with the organic layer from the same bottle, followed by two extractions with ethyl acetate (2 × 1 l.). Each organic extract was washed with water (100 ml.), and the combined extracts from the four bottles were dried and evaporated to leave a gum (47 g.). A solution of this gum in ethanol (400 ml.) was treated with hydrated oxalic acid (50 g.) and warmed to give a mother-liquor *A* and a crop of *O*-methylpsychotrine hydrogen oxalate (41 g.), m. p. 162—163° (decomp.), $[\alpha]_D^{18}$ +43·1° (*c* 3·15 in water). Pyman [2] reports m. p. 150—155° (decomp. at 162°), $[\alpha]_D$ +45·9° (*c* 4·26 in water). The *O*-methylpsychotrine base, recovered from the hydrogen oxalate, crystallised from dry ether as prisms, m. p. 121—123° [lit.,[2] m. p. (corr.) 123—124°].

(b) *Isolation of emetamine.* The combined upper layers from bottles 0 and 1 were concentrated to about 2 l. and then shaken with 0·5M-KH_2PO_4 solution (2 × 1 l.). After the organic layer had been washed and dried, it was evaporated to leave the weakly basic alkaloids (13·5 g.) which have been reserved.

The stronger bases (12 g.), recovered as above from the buffer solution, were dissolved together with hydrated oxalic acid (9 g.) in ethanol (100 ml.). Emetamine hydrogen oxalate (0·54 g.) slowly crystallised; it had m. p. 170—171° (decomp.), $[\alpha]_D^{18}$ −5·5° (*c* 13·4 in water). Pyman [2] records m. p. (corr.) 165—171° (decomp.), $[\alpha]_D$ −6·0° (*c* 3·92 in water). Recovery of

[5] Unpublished work from this laboratory.
[6] Craig, Hausmann, Ahrens, and Harfenist, *Analyt. Chem.*, 1951, **23**, 1236.
[7] *Idem, ibid.*, p. 1326.

the base from the hydrogen oxalate followed by crystallisation from ether gave the emetamine–ether complex, m. p. 142—143° (lit.,[2] m. p. 142—143°).

The mother-liquor from the 0·54 g. of hydrogen oxalate above yielded more emetamine when the base therein was distributed between ethyl acetate and aqueous buffer made from 0·5M-KH_2PO_4 (7 vol.) and 0·5M-K_2HPO_4 (1 vol.) for 85 transfers. Three separate runs were made from one-third of the base in each; initially the base was scattered in the first 5 tubes. The emetamine (K 1·9) was recovered as above from tubes 45—70 in each distribution, and the combined base was purified by crystallisation as the hydrogen oxalate (0·47 g.), m. p. and mixed m. p. with the above sample 170—171°.

The alkaloids from tubes 71—90 of the three runs and from the mother-liquor from the isolation of the 0·47 g. crop of emetamine hydrogen oxalate were recovered as Fraction *B* (4·9 g.).

(c) *Isolation of emetine.* Bottles 6 and 7, by the usual working up, gave a dark brown base (65 g.). A portion (13·2 g.) was dissolved in water by the addition of sufficient 2N-hydrochloric acid to make the solution acid to Congo Red. Addition of ammonium bromide caused the very slow separation of emetine hydrobromide tetrahydrate from which the base (3·03 g.) was recovered into ether as usual. A portion of this was benzoylated [8] to give *N*-benzoylemetine, m. p. and mixed m. p. 184—185°.

Emetine base was isolated in better yield from the 65 g. of crude base above by fractionating a portion (1 g.) in a countercurrent distribution between ethyl acetate and aqueous phosphate buffer made from 0·5M-KH_2PO_4 (3 vol.) and 0·5M-K_2HPO_4 (7 vol.). The bases were scattered initially in the first 3 tubes and 95 transfers were applied. Tubes 45—80 contained the emetine, well separated from the other bases; it was isolated as above (0·29 g.). On conversion into the hydrobromide as above, the colourless salt crystallised (395 mg.; m. p. 253—255°, after previous sintering).

Part of the base (28 mg.), recovered from the emetine hydrobromide, was converted into *N*-benzoylemetine (28·4 mg.), m. p. and mixed m. p. 185—186°.

Isolation of Ipecac-alkaloid A.—A portion of the bases (2·7 g.) from fraction *B* [section (b) above] was distributed for 95 transfers between ethyl acetate and aqueous buffer made from 0·5M-KH_2PO_4 (100 vol.) and 0·5M-K_2HPO_4 (6·3 vol.). The bases were scattered initially in the first 5 tubes of the machine. Analysis showed that the bases were spread throughout the machine, rising in amount to a peak at tube 55. Recovery of the bases was therefore carried out arbitrarily from tubes 0—19, 20—40, 41—45, and 46—50. All were treated separately with hydrated oxalic acid in ethanol, and the second and the third fraction yielded crystals (70 mg., 37 mg. respectively). These were combined and recrystallised from ethanol, to give colourless prisms of ipecac-alkaloid A oxalate, m. p. 182—190° (decomp.) after previous sintering (Found: C, 63·7; 63·3; H, 7·3, 6·9; OMe, 21·8%).

Evidence for instability of Ipecac-alkaloid A, or for the presence of a small amount of impurity in the oxalate, was found when the base was converted into its picrate.

The base (28 mg.), recovered from the oxalate (40 mg.) by aqueous ammonia followed by ether-extraction, was treated with picric acid (30 mg.) in ethanol (40 ml.). When the resulting suspension was boiled for a few min., most of the solid remained undissolved. This solid was collected from the cold alcoholic solution, and the filtrate was evaporated to dryness. The dark residual gum crystallised partially from acetone to give rods (5 mg.), m. p. 149—150°. Recrystallisation of the insoluble picrate from aqueous acetone gave ipecac-alkaloid A picrate as rods (22 mg.), m. p. 195—196° (decomp.) [Found: C, 59·1; H, 5·9; N, 8·9%; equiv. (ultraviolet absorption [9]), 794, 780, 754, 781].

Ipecac-alkaloid A base recovered as above from its oxalate (37 mg.) subsequently crystallised from ether as colourless rosettes of needles (22 mg.), m. p. 143—146°, unchanged on further recrystallisation from ether (Found: C, 71·2; H, 8·2; N, 5·6%).

Isolation of Protoemetine.—The mother-liquor A [section (a) above] was evaporated to dryness and the residue dissolved in water (400 ml.). The solution was made alkaline with potassium carbonate, the alkaloids were extracted into ethyl acetate (total 700 ml.), and the solution was thoroughly washed with water. Evaporation of the dried solution left a gum (14 g.). This was divided into halves and these were distributed in two countercurrent distributions of 92 transfers (base scattered initially in the first 8 tubes) between ethyl acetate and

[8] Carr and Pyman, *J.*, 1914, **105**, 1591.
[9] Cunningham, Dawson, and Spring, *J.*, 1951, 2305.

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aqueous buffer made from 0·5M-KH_2PO_4 (4 vol.) and 0·5M-K_2HPO_4 (1 vol.). Analysis showed a well-separated peak between tubes 45 and 68. The contents of these tubes from the two runs were combined and the base therein was recovered by the method used above. A brown gum (4·7 g.) was obtained which, as a solution in ethanol (31 ml.) and water (38 ml.), was immediately treated with 60% perchloric acid (6 ml.). The precipitated crystals (4·3 g.) were recrystallised from aqueous ethanol, to give *protoemetine perchlorate monohydrate* (4·1 g.) as pale yellow needles, m. p. 140—142° after previous sintering. Further recrystallisation from aqueous ethanol (charcoal) gave the colourless salt of the same m. p. (loss on drying at 110°, 4·0, 4·6. $C_{19}H_{27}O_3N,HClO_4,H_2O$ requires H_2O, 4·1%. Found on dried salt: C, 54·6, 54·3; H, 6·55, 6·5; N, 3·27, 3·28; Cl, 8·46; OMe, 15·3, 14·2; NMe, 0·94; *C*-methyl, 1·9%; equiv. by titration, 412. $C_{19}H_{27}O_3N,HClO_4$ requires C, 54·6; H, 6·7; N, 3·36; Cl, 8·5; 2OMe, 14·8; 1NMe, 6·95; 1*C*-methyl, 3·6%; equiv., 417·7). The anhydrous salt had m. p. 193—195° and $[\alpha]_D^{25}$ −10·9° (*c* 3·13 in ethanol).

Grateful acknowledgment is made to Mr. H. E. Glynn and Messrs. Whiffen and Sons Limited for generous supplies of Ipecacuanha residues, to the Rockefeller Foundation for financial support, and to the Department of Scientific and Industrial Research for a Maintenance Award (to B. J. T. H.).

THE UNIVERSITY, BRISTOL. [*Received, January 7th,* 1959.]

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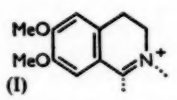
347. *Ipecacuanha Alkaloids. Part II.* The Structure of Protoemetine and a Partial Synthesis of (−)-Emetine.*

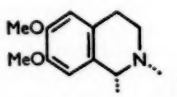
By A. R. BATTERSBY and B. J. T. HARPER.

Protoemetine, a new alkaloid from ipecacuanha root, is shown to have the structure (V; R = CHO) and its properties are described. A partial synthesis of (−)-emetine from protoemetine has been achieved, thus showing that the two alkaloids have the same stereochemistry. The biogenetic significance of protoemetine is discussed.

IT was shown in the preceding paper that ipecacuanha root contains a new, optically active alkaloid which, because of its conversion into emetine (below) and for the biogenetic reasons discussed below, was named protoemetine. The instability of the new base prevented molecular-weight studies; as a result, the following discussion of its chemistry starts with the assumption that its empirical formula, $C_{19}H_{27}O_3N$, is also the molecular formula. This will be subsequently justified.



(I)



(II)

As reported briefly in part,[1] protoemetine contains two methoxyl groups and the Kuhn–Roth oxidation yielded 53% of the theoretical amount of acetic acid from one *C*-methyl group; there is no *N*-methyl group. A negative Labat test showed the absence of methylenedioxy-groups. The ultraviolet absorption is characteristic of a veratrole nucleus and indicates that only one such residue is present in the molecule. Moreover, the alkaloid was readily dehydrogenated by mercuric acetate, which is known to convert many cyclic amines into the corresponding imines [2] and in particular to dehydrogenate tetrahydro*iso*quinolines to the corresponding 3 : 4-dihydro*iso*quinolines.[3] The ultraviolet absorption of

* Part I, preceding paper.

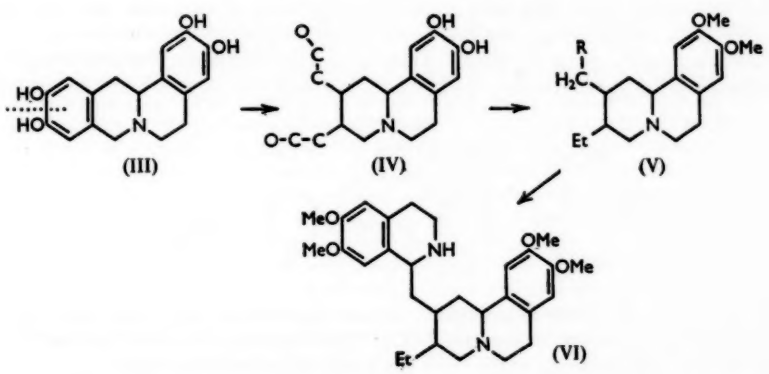
[1] Battersby, Davidson, and Harper, *Chem. and Ind.*, 1957, 983.
[2] Leonard and Hauck, *J. Amer. Chem. Soc.*, 1957, **79**, 5279, with earlier papers and refs. cited therein.
[3] Battersby and Binks, *J.*, 1958, 4333.

the amorphous product showed the typical pattern given by 3 : 4-dihydro-6 : 7-dimethoxy-*iso*quinoline salts (I). It is therefore very probable that the residue (II) is present in protoemetine.

The infrared spectrum of protoemetine perchlorate showed the absence of ester and alkene groups; however, the spectrum strongly indicated the presence of an aldehyde group. This was readily confirmed when the alkaloid gave a positive Tollens reaction and a crystalline semicarbazone. The presence of an aldehyde function explains the marked instability of protoemetine base which was noted in the preceding paper, and why the decomposition is accelerated by alkali.

Acetylation of protoemetine yielded an amorphous basic product, thus showing that the nitrogen atom is tertiary. Also, the basic strength of the alkaloid, as shown by a thermodynamic pK_a in water at 25° of 8·11 ± 0·01, is consistent with structures in which the nitrogen atom is common to two saturated rings. The above pK_a value can be compared with the apparent pK_a values for yohimbine and yohimbane (7·13 and 7·45 respectively), which were determined in 80% Methylcellosolve–water (the thermodynamic pK_a for strychnine [5] in water at 25° is 0·9 unit higher than the apparent pK_a for this alkaloid [6] determined in 80% Methylcellosolve–water). There was no reduction when the alkaloid-free base was shaken with hydrogen and platinum in ethanol, in keeping with the infrared studies above. However, the base perchlorate in the presence of sodium acetate absorbed one mol. of hydrogen with attack at the aldehyde group. No doubt the positive result obtained in the second experiment is due to the effect of acetic acid which is well known to assist hydrogenations.

There are many possible structures for protoemetine which will accommodate the evidence summarised above and the selection of the most probable one rests upon biogenetic considerations. Robinson [7] suggested that emetine (VI) arises by Woodward fission of one catechol residue in the norprotoberberine (III); in the scheme used here, the nature of the product (IV) is left purposely vague. Suitable reduction and *O*-methylation of this intermediate lead to the aldehyde (V; R = CHO) which by condensation with dihydroxy-



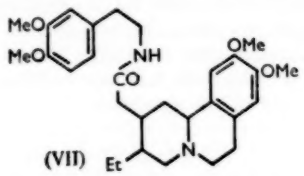
phenylalanine, decarboxylation, and *O*-methylation could reasonably give rise to emetine (VI). This scheme differs from the original one [7] in the order of the necessary reduction, methylation, and condensation steps, but, in effect, it was included in Robinson's proposals since they were not claimed to have sequential significance.

It is obvious that structure (V; R = CHO), $C_{19}H_{27}O_3N$, can explain all the properties

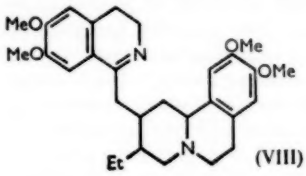
[4] Janot, Goutarel, Le Hir, Amin, and Prelog, *Bull. Soc. chim. France*, 1952, **19**, 1085.
[5] Everett, Openshaw, and Smith, *J.*, 1957, 1120.
[6] Prelog and Häfliger, *Helv. Chim. Acta*, 1949, **32**, 1851.
[7] Robinson, *Nature*, 1948, **162**, 524.

XUM

of protoemetine and attempts were made to confirm this structure by condensing protoemetine with 3 : 4-dimethoxyphenethylamine under the conditions of a Pictet–Spengler reaction. No emetine, *iso*emetine, or their derivatives could be isolated from the product.



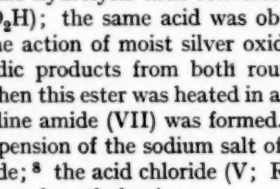
(VII)



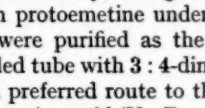
(VIII)

Protoemetine was, however, proved to have the structure (V; R = CHO) in the following way. An amorphous oxime (V; R = CH:N·OH) was readily prepared from the alkaloid and this was dehydrated with hot acetic anhydride to the crystalline nitrile (V; R = CN). Alkaline hydrolysis then converted the nitrile into the corresponding amino-acid (V; R = CO_2H); the same acid was obtained directly, though invariably in much lower yield, by the action of moist silver oxide on protoemetine under a variety of conditions. The acidic products from both routes were purified as the methyl ester (V; R = CO_2Me). When this ester was heated in a sealed tube with 3 : 4-dimethoxyphenethylamine, the crystalline amide (VII) was formed. A preferred route to this amide involved treatment of a suspension of the sodium salt of the amino-acid (V; R = CO_2H) in benzene with oxalyl chloride;[8] the acid chloride (V; R = COCl) so formed then reacted smoothly with 3 : 4-dimethoxyphenethylamine.

The amide (VII) was cyclised in high yield by the use of phosphoryl chloride in boiling toluene, and the crystalline product (VIII) was shown to be identical with natural *O*-methylpsychotrine by comparison of m. p., mixed m. p., and infrared absorption. Also, the crystalline hydrogen oxalates of the natural and the partially synthetic alkaloid had identical m. p., mixed m. p., infrared absorptions, optical rotations, and *X*-ray powder photographs. Since *O*-methylpsychotrine is known with certainty to have the structure (VIII), it follows from the foregoing transformations that protoemetine has the structure (V; R = CHO). *O*-Methylpsychotrine has previously been reduced[9] to (−)-emetine (VI), which is the naturally occurring form. Thus the partial synthesis of *O*-methylpsychotrine represents a partial synthesis of (−)-emetine; it also demonstrates conclusively that the



(IX)



(X)

stereochemistry at the three asymmetric centres of protoemetine is the same as that at the corresponding positions in emetine (VI). The importance of this correlation will be brought out in a forthcoming paper[10] on the stereochemistry of emetine.

The product from hydrogenation of protoemetine must now be assigned the structure (V; R = CH_2·OH) and is named dihydroprotoemetine; it was more readily obtained by reducing protoemetine with sodium borohydride in methanol.

The isolation of protoemetine gives strong support to the proposed mode of biogenesis of emetine[7] since it provides the link between the benzyl*iso*quinolines and the protoberberines on the one hand, and the more complex ipecacuanha alkaloids on the other. In

[8] Adams and Ulich, *J. Amer. Chem. Soc.*, 1920, **42**, 599.
[9] Pyman, *J.*, 1917, **111**, 419; Karrer, Eugster, and Rüttner, *Helv. Chim. Acta*, 1948, **31**, 1219; Battersby and Davidson, unpublished work.
[10] Battersby and Garratt, unpublished work.

this it is a close analogue of corynantheine (IX) in the indole series; this base, however, is the enol ether of an aldehyde. As there is now very strong evidence [11] that " pelletierine " does not have the structure (X) which was originally assigned to it, protoemetine remains as the only known aldehydic alkaloid.

Experimental

General directions are given in the preceding paper. Infrared spectra were determined as Nujol mulls unless otherwise stated.

Spectra.—The infrared spectrum of protoemetine perchlorate monohydrate showed peaks at 2810 cm.$^{-1}$ (aldehyde C–H), 1728 (aldehyde C:O) and 1622 cm.$^{-1}$ (aromatic ring). The ultraviolet absorption of the anhydrous salt in ethanol had $\lambda_{min.}$ 220 and 254, $\lambda_{max.}$ 232 and 283 mμ (log ε 3·85, 2·68, 3·92, 3·61 respectively).

Mercuric Acetate Dehydrogenation of Protoemetine (with G. C. Davidson).—A solution of freshly recovered protoemetine base (25 mg.) in 15% aqueous acetic acid (4 ml.) was boiled under reflux for 5½ hr. with hydrated sodium acetate (10 mg.) and mercuric acetate (0·2 g.). Hydrogen sulphide was then passed through the warm solution until the precipitation of the sulphides was complete. These solids were filtered off and the clear filtrate was evaporated to dryness. Part of the residue (1·2 mg.) was dissolved in water (100 ml.) for determination of the ultraviolet absorption, $\lambda_{min.}$ 229, 276, 326, $\lambda_{max.}$ 247, 303, 352 mμ [cf. the absorption of 3-(3 : 4-dimethoxyphenyl)-3 : 4-dihydro-6 : 7-dimethoxy-1-methyl*iso*quinoline hydrogen oxalate [3]].

Protoemetine Semicarbazone.—A mixture of protoemetine perchlorate monohydrate (0·6 g.) and semicarbazide hydrochloride (0·42 g.) was dissolved in water (6 ml.) and ethanol (1 ml.) at 40°. Hydrated sodium acetate (0·6 g.) was then added portionwise with swirling during 5 min. and the resultant solution was warmed on the water-bath for 15 min. The cooled solution was treated with ether (2 ml.) and made alkaline with ammonia; a gum was precipitated which crystallised (0·48 g.; m. p. 161—166°). Recrystallisation thrice from ethyl acetate gave *protoemetine semicarbazone*, m. p. 168—169° (Found: C, 64·2; H, 8·4; N, 15·2. $C_{20}H_{30}O_3N_4$ requires C, 64·1; H, 8·1; N, 14·95%).

Attempted Acetylation of Protoemetine.—Freshly recovered protoemetine (226 mg.) was heated with acetic anhydride (3 ml.) for 3 hr. at 90°. After distillation of the anhydride, the residue was separated as usual into a neutral (8 mg.) and a basic fraction (94 mg.). Much ether-insoluble polymer was formed.

Dihydroprotoemetine (V; R = CH_2·OH).—(a) *Use of borohydride.* A solution of protoemetine perchlorate (85 mg.) in methanol (5 ml.) was treated portionwise during 1 hr. with sodium borohydride (0·2 g.), then warmed at 60° for 5 min., diluted with water (30 ml.), and extracted thrice with ether, each organic layer being washed with water. Evaporation of the dried ethereal solutions yielded a gum (56 mg.) which afforded the *perchlorate of dihydroprotoemetine* from aqueous ethanol as prisms. After recrystallisation from water, these had m. p. 199—200° (Found: C, 54·2; H, 7·2. $C_{19}H_{30}O_7NCl$ requires C, 54·35; H, 7·2%), $\nu_{max.}$ (broad) 3550 cm.$^{-1}$ (OH) (no carbonyl band).

(b) *Catalytic preparation.* When anhydrous protoemetine perchlorate (13·48 mg.) and sodium acetate (11 mg.) were shaken in ethanol (10 ml.) with Adams platinum and hydrogen at 20·5°/743 mm., there was a steady uptake of hydrogen for the first 7 hr. This was followed by a very slow uptake (linear with time) for the next 23 hr. By extrapolating the slow linear uptake to zero time, the uptake in the more rapid phase was found to be 0·81 ml. (1·01 mol.). When the filtered solution was concentrated, dihydroprotoemetine perchlorate crystallised (7 mg.); after recrystallisation from water, this had m. p. 196—198°. Its infrared spectrum was identical with that of the foregoing product.

2-Cyanomethyl-3-ethyl-1 : 2 : 3 : 4 : 5 : 6 : 7-hexahydro-9 : 10-dimethoxybenzo[a]*quinolizine* (V; R = CN).—A solution of protoemetine perchlorate monohydrate (754 mg.), hydrated sodium acetate (682 mg.), and hydroxylamine hydrochloride (414 mg.) in ethanol (28 ml.) and water (9 ml.) was heated under reflux for 1 hr. Hydroxylamine hydrochloride (0·3 g.) and hydrated sodium acetate (0·7 g.) were then added, followed by the same amounts again of these two reagents after a further 1 hour's heating; the reactants were then heated for 15 hr. After addition of water (27 ml.) to the mixture, the ethanol was evaporated and the aqueous solution

[11] Wibaut and Hirschel, *Rev. Trav. chim.*, 1956 **75**, 225; Bowman and Evans, *J.*, 1956, 2553.

was adjusted to pH 9 with aqueous potassium carbonate. The precipitated oil was extracted into ether, and the solution washed with water, dried, and evaporated to yield protoemetine oxime as a gum (586 mg.). This was heated under reflux with acetic anhydride (5 ml.) for 1 hr. and the anhydride was evaporated. The residue was partitioned between ether and dilute hydrochloric acid, and the aqueous layer, after basification with sodium hydroxide, was extracted thrice with ether. Evaporation of the dried ethereal solution left a gum (514 mg.) of which part (0·15 g.) was distilled at 160° (bath)/0·02 mm. The distillate crystallised from aqueous ethanol to give the *cyanomethyl derivative* (V; R = CN) as needles (135 mg.), m. p. 153·5—154° (Found: C, 72·7; H, 8·3. $C_{19}H_{26}O_2N_2$ requires C, 72·6; H, 8·3%).

Methyl 3-*Ethyl*-1 : 2 : 3 : 4 : 5 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizin*-2-*ylacetate* (V; R = CO_2Me) *and the Corresponding Ethyl Ester* (V; R = CO_2Et).—(a) *From the corresponding nitrile.* The foregoing crude nitrile (364 mg.) was heated under reflux for 72 hr. with a solution (5 ml.) of potassium hydroxide (2·8 g.) in water (2 ml.) and ethanol (9 ml.). After addition of water (20 ml.) to the mixture, it was extracted thrice with ethyl acetate, some inorganic matter separating. This was filtered off, and the filtrate was acidified with hydrochloric acid and evaporated to dryness. The residue was dried overnight at room temperature over phosphoric oxide, and the amino-acid hydrochloride was extracted from the inorganic salts with anhydrous ethanol. Evaporation of the ethanol left a gum which was treated in anhydrous methanol (10 ml.) with concentrated sulphuric acid (0·4 ml.), heated under reflux for 4 hr., cooled, and poured on a mixture of ice and sodium carbonate. The precipitated base was extracted into ether, and the dried ethereal solution was evaporated to a gum (285 mg.). This crystallised from light petroleum (b. p. 40—60°) to give the *methyl ester* (V; R = CO_2Me) as needles (236 mg.), m. p. 96—98°. Distillation of this ester at 150° (bath)/0·01 mm., followed by three recrystallisations from light petroleum, gave the analytical sample, m. p. 98—99° (Found, in material dried at 56°: C, 69·6; H, 8·5. $C_{20}H_{29}O_4N$ requires C, 69·2; H, 8·4%), $[\alpha]_D^{20}$ −35·4° (*c* 2·82 in methanol), $\nu_{max.}$ (in CCl_4) 1740 (s) cm.$^{-1}$ (CO_2Me).

By substituting ethanol for methanol in the above esterification step, the corresponding *ethyl ester* was prepared. Distillation of the crude ester at 140° (bath)/5 × 10^{-4} mm. followed by three recrystallisations of the distillate from light petroleum (b. p. 40—60°) gave needles, m. p. 88—90° (Found, in material dried at 78°: C, 69·6; H, 8·6. $C_{21}H_{31}O_4N$ requires C, 69·75; H, 8·65%), $\nu_{max.}$ (in CCl_4) 1726 (s) cm.$^{-1}$ (CO_2Et).

(b) *Oxidation of protoemetine.* Protoemetine, freshly recovered from its perchlorate (80·8 mg.), was dissolved in 50% aqueous ethanol (12 ml.) and shaken in all for 2 hr. with silver oxide (from 0·4 g. of silver nitrate). Initially the reaction mixture was raised to 50° and shaking was continued without further heating for 1 hr. This process was repeated once. The suspension was then filtered, the solids were washed with warm water, and the filtrate was extracted thrice with ether. Evaporation of the aqueous layer left a gum which was dissolved in methanol (25 ml.); concentrated sulphuric acid (0·5 ml.) was added and the solution was heated under reflux for 2 hr., after which the amino-ester (9 mg.) was isolated and crystallised as above; it had m. p. and mixed m. p. 96—97°.

2-[(N-3 : 4-*Dimethoxyphenethylcarbamoyl*)*methyl*]-3-*ethyl*-1 : 2 : 3 : 4 : 6 : 7-*hexahydro*-9 : 10-*dimethoxybenzo*[a]*quinolizine* (VII).—(a) *From the ester* (V; R = CO_2Me). 3 : 4-Dimethoxyphenethylamine (0·2 g.) and the ester (V; R = CO_2Me) (50 mg.) were heated together in an evacuated sealed tube at 180° for 8 hr.; the mixture was then dissolved in ethyl acetate (20 ml.) and shaken with two portions (20 ml.; 10 ml.) of aqueous buffer made from 0·5M-KH_2PO_4 (11 vol.) and 0·5M-K_2HPO_4 (2 vol.), and the combined aqueous extracts were shaken with ethyl acetate (30 ml.). Evaporation of the combined organic solution left a crystalline residue (58 mg.) which was recrystallised from ethyl acetate, to give the amide (VII) as needles, m. p. 168—170°, raised to 169—170° on admixture with the sample below.

(b) *From the acid chloride* (V; R = COCl). A solution of the ester (V; R = CO_2Me) (117 mg.) in 2N-hydrochloric acid (5 ml.) was heated under reflux for 15 hr., then evaporated to dryness to leave the crystalline amino-acid hydrochloride. This was dried over phosphoric oxide at 100°/0·01 mm. for 3 hr. Part of the hydrochloride (117 mg.) in water (2 ml.) was treated with 0·1N-sodium hydroxide (6·34 ml., 2 equiv.), the solution then evaporated to dryness, and the finely powdered sodium salt, together with sodium chloride, dried as above. A suspension of this mixture (121 mg.) in dry benzene (5 ml.) was stirred at 0° while freshly distilled oxalyl chloride (0·038 ml., 1·5 equiv.) in benzene (1 ml.) was added during 5 min. After 15 min., the ice-bath was removed and the temperature of the mixture was raised to 20° during 1¾ hr.

3 : 4-Dimethoxyphenethylamine (0·3 ml.) was then added with stirring, and the mixture kept overnight. Addition of water (5 ml.) together with an excess of dilute hydrochloric acid gave a solution from which the benzene was evaporated. Some insoluble solid was filtered off and the filtrate was made alkaline with potassium carbonate. The precipitated solid (70 mg.) was recrystallised from ethyl acetate and from 50% aqueous ethanol, to give the *amide* (VII), m. p. 171·5—172·5° (Found: C, 69·5; H, 8·3. $C_{29}H_{40}O_5N_2$ requires C, 70·1; H, 8·1%), $\nu_{max.}$ 3440 and 1652 cm.$^{-1}$ (CO·NH).

Partial Synthesis of (+)-O-*Methylpsychotrine* (VIII).—A solution of the foregoing amide (23 mg.) in anhydrous toluene (2 ml.) was heated under reflux for 1 hr. with freshly distilled phosphoryl chloride (0·15 ml.). Water (10 ml.) was added to the cooled mixture, and the toluene layer was separated and shaken with dilute hydrochloric acid (5 ml.). The combined aqueous solutions were basified with sodium hydroxide and extracted thrice with ether. Evaporation of the dried ethereal solution left a gum (21 mg.) which crystallised from dry ether, to give *O*-methylpsychotrine (17 mg.), m. p. and mixed m. p. with the natural alkaloid 121—122·5°. The infrared spectra of the natural and the partially synthetic alkaloids were identical.

The partially synthetic base was converted into its hydrogen oxalate in the usual way to give the characteristic sheaves of needles, m. p. 151—155° (decomp.) unchanged on admixture with an authentic sample of *O*-methylpsychotrine hydrogen oxalate of the same m. p. (Found, in material dried at 110°: C, 56·6; H, 6·4. Calc. for $C_{33}H_{46}O_{12}N_2,2H_2O$: C, 57·0; H, 6·7%. Found, in authentic *O*-methylpsychotrine hydrogen oxalate dried under the same conditions: C, 56·4; H, 6·6%). $[\alpha]_D$ of the " synthetic " salt was +43·8° (*c* 2·10 in water); $[\alpha]_D$ of authentic *O*-methylpsychotrine hydrogen oxalate determined under the same conditions was +43·2° (*c* 2·02 in water). The identity of the natural and the partially synthetic hydrogen oxalate was further established as described on p. 1750.

Our thanks are expressed to Dr. H. T. Openshaw and Dr. A. J. Everett for the microtitration on protoemetine, to Dr. R. Binks for some experiments on the oxidation of protoemetine, and to the Department of Scientific and Industrial Research for a Maintenance Award (to B. J. T. H.).

THE UNIVERSITY, BRISTOL. [*Received, January 7th,* 1959.]

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348. *Tritylation of* ortho-*Disubstituted Benzenes. Systematic Differences of Activation of* ortho- *and* para-*Directing Groups.*

By GABRIEL CHUCHANI.

As tritylation of aromatic compounds may involve direct attack of the triphenylmethylcarbonium ion on the benzene ring, this investigation was directed towards showing the differing directive influences of strongly activating substituents in disubstituted benzenes. In all cases only one trityl group entered the ring. The relative directing powers were: OH > NH_2 > NHAc > OMe > Me.

SINCE resonance would considerably stabilise the triphenylmethylcarbonium ion, its direct attack on the benzene ring should be rather slow and occur at a position of high electron density. The present work was directed to show that the trityl group may react only at one point where there is a difference of electron density due to a pair of activating groups which thus control the orientation control of this product. In a compound *o*-C_6H_4YZ a triphenylmethyl will enter *para* to whichever of Y or Z controls the reaction.

ortho-Disubstituted benzenes were chosen because the opposite side of each activator is free for substitution. Though adjacent substitution occurs in some cases with the *meta*- and *para*-disubstituted isomers,[1-3] this will not happen readily with the bulky trityl

[1] Schorigin, *Ber.*, 1927, **60**, 2373.
[2] Boyd and Hardy, *J.*, 1928, 630.
[3] Hardy, *J.*, 1929, 1000.

group. Further, change in temperature changes the result.[1-4] It was also found that hydrochloric acid used as catalyst may convert the triphenylmethanol into 9-phenylfluorene without affecting the aromatic compound.

The Table shows that of the compounds studied only two, *o*-acetanisidide and *o*-aminoacetanilide, did not react with triphenylmethanol: however, electrophilic attack of triphenylmethyl chloride alone on aromatic compounds occurs under favourable conditions,[4,5] and the products to be expected from these two compounds were thus obtained in our work.

The only tritylated products previously reported were made from *o*-toluidine [3,6] and *o*-cresol [4] with hydrochloric acid, and from *o*-methylanisole [2] and *o*-cresol [1,2,7] with sulphuric

Tritylation of ortho-*disubstituted benzenes.*[c]

No.	Compound	Time	Temp.	M. p. Found	M. p. Lit.	Yield (%)	Posn. of CPh_3
1	*o*-Cresol *	3 days	B. p.	182—183°	182—183° [7]	87	4 (OH = 1)
2	*o*-Cresol	1 day	Room	182—183	,,	84	,,
3	*o*-Toluidine *	6 hours	B. p.	215—216	216 [3]	79	4 (NH_2 = 1)
4	*o*-Toluidine	2 hours	B. p.	215—216	,,	76	,,
5	*o*-Acetotoluidide *	2 days	B. p.	215—216	,,	84	,,
6	*o*-Acetotoluidide	7 days	70—75°	261—262	—	51	4 (NHAc = 1)
7	*o*-Acetotoluidide	2 days	80°	93	93·0—93·5 [4]	42	[a]
8	*o*-Methylanisole *	4 days	B. p.	165—166	165 [2]	86	4 (OMe = 1)
9	*o*-Methylanisole	2 hours	80—85°	165—166	165 [2]	92	,,
10	*o*-Acetanisidide *	3 days	B. p.	184—185	185—186 [8]	83	4 (NH_2 = 1)
11	*o*-Acetanisidide	4 days	65°	93	93·0—93·5 [4]	36	[a]
12	*o*-Anisidine *	3 days	B. p.	184—185	185—186 [8]	80	4 (NH_2 = 1)
13	*o*-Anisidine	4 hours	B. p.	184—185	185—186 [8]	65	,,
14	*o*-Anisidine HCl	4 days	B. p.	184—185	185—186 [8]	74	,,
15	Guaiacol *	4 days	B. p.	188—189	—	76	4 (OH = 1)
16	Guaiacol	1 day	Room	188—189	—	81	,,
17	*o*-Aminoacetanilide *	4 days	B. p.	144—145	144 [9]	47	[b]
18	*o*-Aminoacetanilide	2 days	65°	93	93·0—93·5 [4]	33	[a]
19	*o*-Hydroxyacetanilide *	2 days	B. p.	286—288	—	82	4 (OH = 1)
20	*o*-Hydroxyacetanilide	4 days	65—72°	272—273	—	36	,,
21	*o*-Aminophenol *	3 days	B. p.	286—288	—	85	,,
22	*o*-Aminophenol	2 days	B. p.	286—288	—	71	,,
23	*o*-Aminophenol HCl †	4 days	B. p.	286—288	—	76	,,
24	*o*-Phenylenediamine	2 days	B. p.	256—257	—	77	4

* In cases thus marked, HCl was the catalyst; † indicates no catalyst; in the others, H_2SO_4. [a] Product was $CHPh_3$; Benkeser and Schroeder (*J. Org. Chem.*, 1958, **23**, 1059) reported also two other hydrocarbons. [b] Product was 9-phenylfluorene. [c] NHAc hydrolysed to NH_2, except Nos. 6 and 20.

No.	Found (%) C	Found (%) H	Found (%) N	Formula	Required (%) C	Required (%) H	Required (%) N	Solvent for crystn
15	85·1	6·0	—	$C_{26}H_{22}O_2$	85·2	6·05	—	AcOH
16	85·1	6·1	—	,,	,,	,,	—	,,
19	84·7	6·5	4·1	$C_{25}H_{21}ON$	84·95	6·6	4·0	Xylene
20	82·2	6·1	3·7	$C_{27}H_{23}O_3N$	82·4	5·9	3·6	C_6H_6
21	85·2	6·7	3·85	$C_{25}H_{21}ON$	84·95	6·6	4·0	Xylene
22	84·8	6·5	3·9	,,	,,	,,	,,	,,
23	84·6	6·7	3·9	,,	,,	,,	,,	,,
24	86·9	6·4	6·3	$C_{25}H_{22}N_2$	87·2	6·4	6·4	EtOH

acid as catalyst. The same products were obtained by us with both catalysts. Hardy [3] assumed, without proof, that the products on tritylation of guaiacol were 4- and 5-tritylguaiacol, but only 4-tritylguaiacol was isolated in our work. While our work was in

[4] MacKenzie and Chuchani, *J. Org. Chem.*, 1955, **20**, 336.
[5] Hart and Cassis, *J. Amer. Chem. Soc.*, 1954, **76**, 1634.
[6] van Alphen, *Rec. Trav. chim.*, 1927, **46**, 501.
[7] Iddles, French, and Mellon, *J. Amer. Chem. Soc.*, 1939, **61**, 3192.

progress, tritylation of *o*-anisidine was reported,[8] with slight variations of isolation and structural proof of the product.

The relative directive influences for tritylation were: OH > NH_2 > NHAc > OMe > Me. This is the same as in inorganic electrophilic substitution into aromatic compounds, except that there NH_2 > OH. The anomaly may result from the circumstance that the concentration of free amine available for reaction is reduced by salt formation.

Experimental

General Procedure.—Triphenylmethanol (1 mol.) was mixed with slightly more than 1 mol. of the compound to be tritylated. For 0·01 mole of the alcohol, about 2 ml. of concentrated sulphuric acid or 4 ml. of concentrated hydrochloric acid and 50 ml. of glacial acetic acid were added. Products were isolated by pouring the mixture into a large amount of cold water. When the compound contained an amino-group, the aqueous mixture was treated with 20% sodium hydroxide solution until no more precipitate was formed. Results are in the Table.

4-*Trityl*-o-*acetanisidide.*—Triphenylmethyl chloride (2·8 g.) was heated with *o*-acetanisidide (1·8 g.) at 135—140° for 8 hr., without solvent. The resulting solid mass, recrystallised from acetic acid, had m. p. 206—207° (3·1 g., 76%) (Found: C, 82·2; H, 6·1; N, 3·4. Calc. for $C_{28}H_{25}O_2N$: C, 82·5; H, 6·2; N, 3·4%).

2-*Amino*-5-*tritylacetanilide.*—Triphenylmethyl chloride (2·8 g.) and *o*-aminoacetanilide (1·7 g.) were heated at 155—160° for 22 hr. The resulting solid was treated with 10 ml. of 20% sodium carbonate solution and crystallised from toluene; it had m. p. 297—299° (1·9 g., 48%) (Found: C, 82·3; H, 6·2; N, 7·0. Calc. for $C_{27}H_{24}ON_2$: C, 82·6; H, 6·2; N, 7·1%).

9-*Phenylfluorene.* Acetic acid (50 ml.) containing concentrated hydrochloric acid (4 ml.) and triphenylmethanol (2·7 g.) was refluxed for 4 days, then poured into water; the resulting solid (1·2 g., 44%), recrystallised from ethanol, had m. p. 144—145° alone or mixed with the product obtained by Kliegl's method.[9]

Proof of Structures.—Acetylation of 4-*trityl*-o-*toluidine.* 4-Trityl-*o*-toluidine (2·0 g.), acetic acid (20 ml.), and acetic anhydride (10 ml.) were refluxed for 6 hr., then poured into water (100 ml.). The solid (1·8 g., 82%), recrystallised from xylene, had m. p. 261—262° alone or mixed with the compound obtained by tritylation of *o*-acetotoluidide.

Hydrolysis of 4-*trityl*-o-*acetotoluidide.* 4-Trityl-*o*-acetotoluidide (2 g.), acetic acid (20 ml.), and concentrated hydrochloric acid (4 ml.) were refluxed for 8 hr., then poured into water (100 ml.). The solid (1·3 g., 72%), recrystallised from ethanol, had m. p. 215—216° alone or mixed with the product formed by tritylating *o*-toluidine.

Deamination of 4-*trityl*-o-*anisidine.* To 4-trityl-*o*-anisidine (2 g.) in acetone (100 ml.), 50% hypophosphorous acid (100 ml.), and concentrated hydrochloric acid (4 ml.) at 0—2°, a slight excess of sodium nitrite was added. The mixture was stirred for 4 hr. and kept overnight at 0°. The product, *m*-tritylanisole, was filtered off after dilution with water and crystallised from acetic acid; it had m. p. 168—169° (1·1 g., 58%) (Found: C, 89·0; H, 6·5. Calc. for $C_{26}H_{22}O$: C, 89·1; H, 6·3%).

m-*Tritylanisole.* The Grignard reagent from *m*-bromoanisole was condensed with triphenylmethyl chloride in the conventional manner under nitrogen. The product, *m*-tritylanisole, crystallised from acetic acid and had m. p. 168—169° (46%), not depressed on admixture with the deamination product of 4-trityl-*o*-anisidine.

Acetylation of 4-*trityl*-o-*anisidine.* 4-Trityl-*o*-anisidine gave, as above, the acetyl derivative (77%), m. p. 206—207° (from acetic acid) alone or mixed with the product obtained from triphenylmethyl chloride and *o*-acetanisidide.

Hydrolysis of 4-*trityl*-o-*acetanisidide.* This material was hydrolysed as described above. The mixture was poured into water and treated with 20% sodium hydroxide solution (~10 ml.). The solid (83%), recrystallised from benzene, had m. p. 184—185° alone or mixed with that obtained by tritylation of *o*-anisidine.

4-*Tritylguaiacol from* 4-*trityl*-o-*anisidine.* 4-Trityl-*o*-anisidine (3 g.) was dissolved in acetone (200 ml.) and water (50 ml.). Concentrated sulphuric acid (5 ml.) was slowly added,

[8] Benkeser and Gosnell, *J. Org. Chem.*, 1957, **22**, 327.
[9] Kliegl, *Ber.*, 1905, **38**, 284.

then at 0—2° sodium nitrite in slight excess. The mixture was stirred for 2 hr. and kept for 6 hr. at 0°. The diazonium salt solution was diluted with water (100 ml.), and the acetone evaporated on a water-bath. Concentrated sulphuric acid (10 ml.) was added and the whole boiled for 1 hr. The resulting gum solidified, and gradually recrystallised from acetic acid–water. Sublimation gave 0·9 g. (30%) of 4-tritylguaiacol, m. p. 188—189° alone or mixed with the product obtained by tritylation of guaiacol.

m-*Tritylaniline*. This was prepared as described by Benkeser and Gosnell.[10]

m-*Tritylacetanilide*. Prepared by acetylation of *m*-tritylaniline as described above and recrystallised from toluene, this product (86%) melted at 167—168° (Found: C, 85·6; H, 6·1; N, 3·8. Calc. for $C_{27}H_{23}ON$: C, 85·9; H, 6·1; N, 3·7%).

Deamination of 2-*Amino*-5-*tritylacetanilide*. This compound was deaminated as described for the 4-trityl-*o*-anisidine. The solid (54%) crystallised from toluene had m. p. 167—168° alone or mixed with *m*-tritylacetanilide.

Hydrolysis of 2-*amino*-5-*tritylacetanilide*. The acetyl group was cleaved as described above. Recrystallisation from ethanol gave the 4-trityl-*o*-phenylenediamine (64%), m. p. of 256—257° alone or mixed with the substance obtained by tritylation of *o*-phenylenediamine.

4-*Trityl*-*o*-*phenylenediamine*. 2-Nitro-4-tritylaniline [10] (0·01 mole) was heated in ethanol (50 ml.) and 20% sodium hydroxide solution (4 ml.) for 4 hr. while zinc dust (6 g.) was added with stirring. The mixture was filtered while hot, and most of the solvent removed in a vacuum. Cooling and recrystallisation from ethanol gave the product (79%), m. p. 256—257° alone or mixed with the product obtained by tritylation of *o*-phenylenediamine and by hydrolysis of 2-amino-5-tritylacetanilide.

2-*Amino*-4-*tritylphenol*. Ethanol (200 ml.), concentrated hydrochloric acid (30 ml.), and 2-nitro-4-tritylphenol [11] were heated, while tin (6 g.) was added during 0·5 hr. Refluxing with stirring was continued for 8 hr.; the solution was filtered and two-thirds of the solvent removed by distillation. Water (200 ml.) was added and then 20% sodium hydroxide solution until no more precipitation occurred. The crystals were filtered off and after recrystallisation from xylene, had m. p. of 286—288° (2·6 g., 70%) alone or mixed with the product resulting from tritylation of *o*-aminophenol or *o*-aminophenol hydrochloride.

Hydrolysis of 2-*hydroxy*-5-*tritylacetanilide*. The acetyl group of this material (0·01 mole) was cleaved as described above. The acetic acid solution was diluted with water (200 ml.), and 20% sodium hydroxide solution (~10 ml.) was added. The solid, crystallised from xylene, had m. p. 286—288° (79%) alone or mixed with 2-amino-4-tritylphenol obtained by tritylation of *o*-aminophenol or its hydrochloride and or by reduction of 2-nitro-4-tritylphenol.

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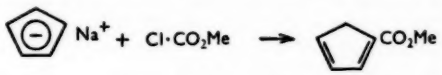
[10] Benkeser and Gosnell, *J. Amer. Chem. Soc.*, 1956, **78**, 4914.
[11] von Zincke and Wugk, *Annalen*, 1908, **363**, 284.

349. *The Cyclopentadienyl Anion. Part I. 1,2-Dimethoxycarbonylcyclopentadienylsodium, a Stabilised Cyclopentadienyl Anion.*

By David Peters.

The compound mentioned in the title has been synthesised and shown to be stable in neutral or alkaline aqueous solution for several hours and in the atmosphere for many weeks. It is a new example where a cyclopentadienyl anion is stabilised by formally neutral substituents.

In examining the structure of methyl cyclopenta-1,3-dienecarboxylate (I) (following paper), a new preparative method for this compound was investigated, namely:

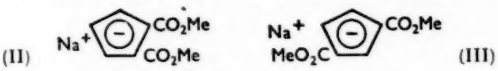


(I)

The expected product (I) was obtained, but in low yield (20—30%), and a second product is formed. This paper is concerned with the structure and properties of the latter.

During the addition of the chloroformate, the solution, originally violet, becomes bright green at the half-way stage and brick-red when addition is complete. Acidification and distillation gives ~25% yields each of the expected ester (I) and a high-boiling material. About half of the organic material is lost.

Working up the mixture without hydrolysis gives a brick-red solid (~20% yield) which is shown below to be 1,2-dimethoxycarbonylcyclopentadienylsodium (II).



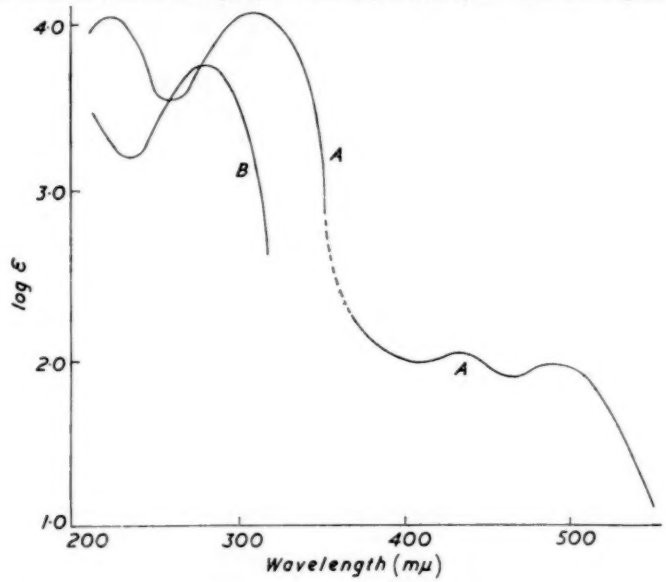
Elementary analysis and molecular-weight determinations show that the compound is monomeric and contains two carboxyl residues and one atom of sodium per cyclopentadienyl residue. If we assume five-fold symmetry of the unsubstituted anion, there are only two possible structures (II) and (III). In acid solution, the red solid is protonated to give a neutral dimethyl cyclopentadienedicarboxylate, probably (IV). Hydrogenation (Raney nickel) of this material in ethanol–benzene led to the uptake of one mol. of hydrogen

to give, in 75% yield, a single sharp-boiling oily fraction which was not identified positively but is believed to be a dimethyl cyclopentenedicarboxylate (the structure of this compound was not examined in detail since only three of the six possible cyclopentenedicarboxylic acids are known). Further hydrogenation (Raney nickel) of this fraction in ethanol afforded the oily saturated ester which on acidic hydrolysis gave the known crystalline *cis*-cyclopentane-1,2-dicarboxylic acid (V). The overall yield of this acid was low (~20%) but several stages are involved and there is no indication of the presence of isomers, so it is assumed that the red solid is substantially a single compound.

There is no doubt then that the two methoxycarbonyl groups are intact and in the 1,2-position. It remains to establish whether the sodium atom is firmly bonded to the organic fragment, as in ferrocene and the organolithium compounds, or whether it is free. The following three-fold evidence shows that the ions are free, certainly in water and very probably in the other solvents and in the solid state: (*a*) The solid does not melt; it is soluble in polar solvents and insoluble in non-polar solvents. (*b*) Lead and barium salts are formed by double decomposition in water; they have the same colour as the

sodium salt. (*c*) The electrical conductivity of the aqueous solution is that of a 1 : 1 electrolyte. At first sight it may seem that the solubility and conductivity data may be accounted for by supposing that the anion (A^-) reacts rapidly with water: $A^- + H_2O \rightleftharpoons AH + OH^-$. This equilibrium would certainly lie far to the right with the unsubstituted anion, but that this cannot be the case for the substituted one is shown by three further points: (i) the concentrated aqueous solution is neutral or at most slightly alkaline; (ii) extraction of the neutral aqueous solution with organic solvents removes nothing; (iii) the electrical conductivity of the aqueous solution at infinite dilution (Λ_0 81 ohm^{-1} $cm.^2$) is very different from that of sodium hydroxide (Λ_0 250 ohm^{-1} $cm.^2$). Thus the compound is ionic.

Absorption spectra of 1,2-*dimethoxycarbonylcyclopentadienylsodium* (*A*) *in neutral or alkaline aqueous solution, in ethanol, and in tetrahydrofuran, and* (*B*) *in* 0·1N-*hydrochloric and -sulphuric acid.*

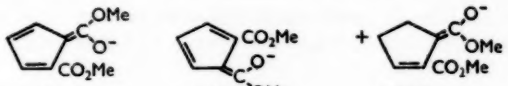


The ultraviolet spectrum of the anion in neutral or alkaline aqueous solution (see Figure) shows two intense peaks, at 225 and 310 mμ, and there is weak adsorption in the 435 and 490 mμ regions. Protonation of the anion leads to a marked change in the position of the bands and in the general appearance of the spectrum. Extraction of the acidified aqueous solution removes the protonated species, as shown by the spectrum of the organic phase.

Discussion.—The unsubstituted cyclopentadienyl anion reacts vigorously with hydroxylic solvents, oxygen, and nucleophiles generally. The introduction of two carboxyl groups stabilises the anion to these reagents. This stabilisation may be expressed in valence-bond terminology by saying that the forms (VI) and (VII) contribute substantially to the wave function of the ground state of the substituted anion while forms such as (VIII) contribute little to the wave function of the neutral butadienyl grouping in (IV). This accords well with current ideas of sacrificial and isovalent resonance,[1] compound (VIII) being a high-energy form since one double bond has been lost. In the substituted anion there is isovalent resonance between three structures with the same number of double bonds (II, VI, VII) and, presumably, comparable energies.

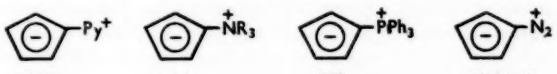
[1] Muller and Mullikan, *J. Amer. Chem. Soc.*, 1958, **80**, 3489.

This ion and that isolated by Linn and Sharkey (see below) differ in an important respect from the earlier examples[2] of stabilised cyclopentadienyl anions (IX—XII) where



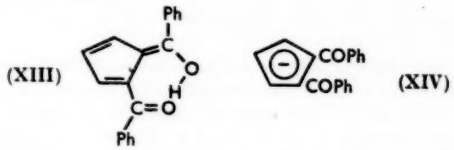
(VI) (VII) (VIII)

the molecules as a whole are electrically neutral although structures with charge separation may be the most important contributors to the wave functions. The present example, and Linn and Sharkey's, show that stabilisation can be achieved by electrically neutral substituents. It appears that one positively charged substituent is about equal to two



(IX) (X) (XI) (XII)

methoxycarbonyl groups and it is noteworthy that this is the ratio which would be expected if the inductive effects of the groups are the predominant factor.[3] The inductive effect of a nitro-group approaches that of a positively charged substituent, and the mononitro-derivative is indeed stable.[4]



(XIII) (XIV)

The similar anion was reported by Linn and Sharkey [5] when they obtained compound (XIII), presumably *via* the anion (XIV); they also prepared the sodium and the potassium salt of the di-*p*-chloro-analogue.

Experimental

Tetrahydrofuran was refluxed and distilled over sodium until the sodium remained clean. Ultraviolet spectra were recorded on a Hilger Uvispek. Raney nickel was prepared as described elsewhere.[6]

Preparation of 1,2-*Dimethoxycarbonylcyclopentadienylsodium*.—Methyl chloroformate (94 g., 1·0 mole) was added dropwise to a stirred solution of cyclopentadienylsodium (1·0 mole, from sodium, 24 g., and cyclopentadiene, 70 g.) in dry tetrahydrofuran (600 c.c.) under dry nitrogen at 0°. The solvent was removed at reduced pressure and the residue was shaken repeatedly with dry ether (1 l.). The ether was removed from the filtrate and the residue distilled, to give methyl cyclopenta-1,3-dienecarboxylate (23 g., 0·2 mole), b. p. 110—130°/15 mm., which partly solidified in 30 min. Crystallisation from light petroleum (b. p. 60—80°) gave the dimer, Thiele's ester (8 g.), m. p. and mixed m. p. 82—83°. The red ether-insoluble residue (92 g.) was extracted (Soxhlet) for 16 hr. with ethyl acetate. The buff-coloured residue (45 g., 0·77 mole) was sodium chloride (95% pure by chloride assay). The ethyl acetate extracts were evaporated at reduced pressure until free from solvent, giving a pink solid (44 g.), free from chloride. This material was extracted (Soxhlet) for 2 weeks with chloroform, the extracted material being removed each day. Fourteen fractions of 1,2-*dimethoxycarbonylcyclopentadienylsodium* (34 g.) were obtained. Fractions 3—12 were identical in appearance [Found, for

[2] Lloyd and Sneezum, *Chem. and Ind.*, 1955, 1221; Ramirez and Levy, *J. Org. Chem.*, 1956, **21**, 488, 1333; *J. Amer. Chem. Soc.*, 1957, **79**, 67, 6167; Spooncer, *Diss. Abs.*, 1956, **16**, 458.
[3] Peters, *J.*, 1957, 2654.
[4] Thiele, *Ber.*, 1900, **33**, 666.
[5] Linn and Sharkey, *J. Amer. Chem. Soc.*, 1957, **79**, 4970.
[6] Paul and Hilly, "Newer Methods of Organic Chemistry," Interscience Publ. Inc., New York, 1948, p. 65.

fraction 3: C, 52·2; H, 4·8; Na, 10·5. For fraction 8: C, 52·1; H, 4·6; Na, 10·5%; *M* (cryoscopic in H_2O), 200. $C_9H_9O_4Na$ requires C, 52·9; H, 4·4; Na, 11·3%; *M*, 204 (van't Hoff *i* factor = 2)].

Hydrogenation of 1,2-*Dimethoxycarbonylcyclopentadienylsodium*.—The sodium compound (5 g.) in water (200 c.c.) and ethanol (50 c.c.) was shaken with benzene (75 c.c.), sulphuric acid (5 c.c. in 20 c.c. of water) was added to the emulsion, and the mixture extracted immediately. Further extraction with benzene (2 × 25 c.c.) gave a red benzene solution which was dried briefly (Na_2SO_4) and diluted with ethanol (50 c.c.). Hydrogenation over Raney nickel at atmospheric pressure led to the uptake of 600 c.c. of hydrogen (theory 550 c.c.) in 2 hr. Filtration and distillation gave a dimethyl cyclopentenedicarboxylate (3·4 g., 75%), b. p. 134—136°/14 mm. (Found: C, 58·7; H, 6·7. Calc. for $C_9H_{12}O_4$: C, 58·7; H, 6·6%), which decolorised potassium permanganate in acetone immediately. An ethereal solution of this oil was extracted thoroughly with sodium carbonate solution. Extraction of the acidified aqueous solution with chloroform gave only a trace of solid. The ester (2·4 g.) was recovered by drying and distilling the ethereal layer. Hydrolysis of the ester with acid or base gave a mixture of acids, m. p. 160—170°. The ester (1·8 g.) was hydrogenated in ethanol (50 c.c.) over Raney nickel, taking up 240 c.c. of hydrogen (theor. 224 c.c.) in 2 hr. Distillation gave *dimethyl* cis-*cyclopentane*-1,2-*dicarboxylate* (1·2 g.), b. p. 125—126°/15 mm. (Found: C, 57·9; H, 8·0. $C_9H_{14}O_4$ requires C, 58·1; H, 7·6%). Refluxing this ester (1·2 g.) with concentrated hydrochloric acid (2 c.c.) for 30 min. and cooling to 0° gave a white solid (0·8 g.), m. p. 115—125°. Two crystallisations from ethyl acetate gave *cis-cyclo*pentane-1,2-dicarboxylic acid (0·5 g.), m. p. and mixed m. p. 133—135°. Refluxing the acid with aniline and pouring the mixture into cold dilute sulphuric acid gave the anil, m. p. and mixed m. p. 88—89° (from aqueous ethanol). Refluxing the acid with acetic anhydride for 2 hr. and distilling the product gave the anhydride, m. p. 75° (lit.,[7] 73°).

Lead and Barium Salts from 1,2-*Dimethoxycarbonylcyclopentadienylsodium*.—The sodium salt (0·3 g.), dissolved in water (1 c.c.), was treated with 1 c.c. of a M-solution of lead acetate or barium chloride. The red precipitate was centrifuged off, washed several times with water, and filtered, giving the *lead* (Found: C, 37·5; H, 3·4; Pb, 36·1. $C_{18}H_{18}O_8Pb$ requires C, 38·0; H, 3·2; Pb, 36·4%), and the *barium salt* (Found: C, 43·4; H, 4·3; Ba, 26·8. $C_{18}H_{18}O_8Ba$ requires C, 43·3; H, 3·6; Ba, 27·45%). Silver, mercuric, and cupric salts gave intractable oily precipitates and complex colour changes, presumably due to oxidation of the organic anion by the metal ions.

Conductivity of Aqueous Solutions of 1,2-*Dimethoxycarbonylcyclopentadienylsodium*.—The conductivity of 0·1—0·0005M-solutions at 25° gave a straight line plot of Λ against $\sqrt{c}$ from which a Λ_0 of 81 ohm^{-1} $cm.^2$ was calculated.

pH *of Aqueous Solutions of* 1,2-*Dimethoxycarbonylcyclopentadienylsodium*.—The pH of freshly prepared aqueous solutions (0·1, 0·01, and 0·001M) were measured on a Pye Universal pH meter. All solutions had pH 7·4—7·6.

Preparation of Authentic cis-*Cyclopentane*-1,2-*dicarboxylic Acid*.—*cis*-Cyclopentene-1,2-dicarboxylic acid, prepared by Nandi's method,[8] as modified by Gupta and Saha,[9] had m. p. 178° (Found: C, 53·9; H, 5·3. Calc. for $C_7H_8O_4$: C, 53·85; H, 5·2%). It did not take up hydrogen over Raney nickel but took up the calculated quantity slowly over platinum to give *cis*-cyclopentane-1,2-dicarboxylic acid, m. p. 133—135° (lit.,[7,10] 140°; 131—133°) (Found: C, 53·3; H, 6·5. Calc. for $C_7H_{10}O_4$: C, 53·2; H, 6·4%). The anil, prepared as described above, had m. p. 88—89° (lit.,[10] 88°) (Found: C, 72·3; H, 6·1; N, 6·8. Calc. for $C_{13}H_{15}O_2N$: C, 72·6; H, 6·1; N, 6·5%).

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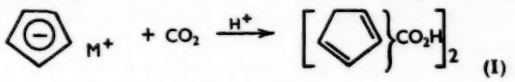
[7] Perkin, *Ber.*, 1885, **18**, 3250; *J.*, 1887, **51**, 240; 1894, **65**, 572.
[8] Nandi, *J. Indian Chem. Soc.*, 1934, **11**, 213.
[9] Gupta and Saha, *ibid.*, 1952, **29**, 331.
[10] Blomquist and Kwiatek, *J. Amer. Chem. Soc.*, 1951, **73**, 2100.

350. *Cyclopentadienecarboxylic Acid. The Structure of the Monomer and the Dimers.*

By David Peters.

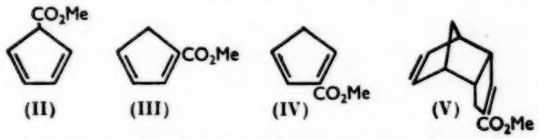
Spectroscopic evidence suggests that Thiele's dimer [1a] of cyclopentadienecarboxylic acid has a structure in which each carboxyl group is conjugated with a double bond. An isomeric dimer with one conjugated and one unconjugated carboxyl group has been isolated. The spectroscopic data support the chemical evidence [2] that methyl cyclopentadienecarboxylate exists exclusively or very largely as the 1 : 3-diene. It is suggested that a reversible prototropic shift occurs in the dimerisation and depolymerisation.

Simple derivatives of cyclopentadiene are attractive as intermediates for the synthesis of non-alternant hydrocarbons containing five-membered rings, an approach used by Hafner [3] in his azulene synthesis. A number of such derivatives is already known [1,4] and of these, the most promising for further synthetic work is the carboxylic acid (I) or its esters, first prepared by Thiele.[1a] The free acid is readily obtained by carboxylating



(I)

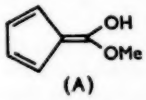
the potassium,[1a,5] sodium,[6] or Grignard [4] derivative of the cyclopentadienyl anion (M = K, Na, or MgX). The point of attachment of the carboxyl group is one of the subjects of this paper. The carboxylic acid is not isolated as such but as the dimer, formed by Diels–Alder dimerisation analogous to that which cyclopentadiene itself undergoes. The dimethyl ester of the dimeric acid is easily obtained by the conventional acid-catalysed esterification: an alternative preparation is described in the following paper.



(II) (III) (IV) (V)

It is known that the dimeric ester, like cyclopentadiene itself, may be depolymerised thermally to the monomeric ester and it has now been shown that this monomer can be stored as a solid at −70° or in dilute solution in organic solvents at room temperature, for several hours. Chemical evidence for the structure of this monomer has been presented by Alder *et al.*,[2] and spectroscopic evidence is now provided which supports their findings. Spectroscopic evidence for the structure of the dimer has also been obtained and these results suggest that the relation between the monomer and the dimer is not simple.

Structure of the Monomeric Ester.—That the monomer is the ester of a cyclopentadienecarboxylic acid is probable from its preparation and this has been confirmed by its hydrogenation to methylcyclopentanecarboxylate. The ultraviolet spectra of the monomer and the dimer confirm that polymerisation and depolymerisation do occur. As Alder and Holtzrichter point out,[7] there are three possibilities (II—IV) for the monomer and it must also be established that it is not a mixture. Alder *et al.*[2] treated this monomer with cyclopentadiene and obtained compound (V), suggesting that the monomer is (III). The ultraviolet spectrum of the monomer provides further evidence for this structure (Fig. 1).



(A)

[1] Thiele, *Ber.*, (*a*) 1901, **34**, 68; (*b*) 1900, **33**, 666.
[2] Alder, Flock, Hausweiler, and Reeber, *Chem. Ber.*, 1954, **87**, 1752.
[3] Hafner, *Annalen*, 1957, **606**, 79.
[4] Courtot, *Ann. Chim.* (*France*), 1915, **4**, 75.
[5] Süs, *Annalen*, 1944, **556**, 85.
[6] Ziegler, Kuhlhorn, and Hafner, *Chem. Ber.*, 1956, **89**, 434.
[7] Alder and Holtzrichter, *Annalen*, 1936, **524**, 147.

The single smooth peak at 274 mμ * suggests that only one compound is present: the bathochromic shift of **36** mμ from the peak of cyclopentadiene itself cannot be reconciled with structure (II) since this should show little or no shift. The examples in the Table show that a bathochromic shift of **27—33** mμ is usual for a carboxyl group in the **1**-position of the butadienyl system, so structure (III) is acceptable. To exclude structure (IV) is more difficult, since only one example (*H* in the Table) is available with the carboxyl group in the 2-position. This case gives a bathochromic shift of **3** to **8** mμ and it can be predicted [9]

FIG. 1. FIG. 2.

FIG. 1. *Absorption spectra of* (*a*) *cyclopentadiene and* (*b*) *methyl cyclopenta-1,3-dienecarboxylate.*

FIG. 2. *Adsorption spectra of:* (*c*) *Thiele's ester* (VII) *and acid*; (*d*) *the dihydro-derivative* (IX), *the second isomer* (X), *the compound* (V) *and its dihydro-derivative* (*the spectra of these compounds are essentially the same: exact values for* λ *and* ε *are in the Experimental section*); *and* (*e*) *resolved peak in Thiele's ester* (*from curve c and curve d*).

on theoretical grounds that the bathochromic shifts of simple substituents in the **1**- and the 2-position of the butadienyl system are in the ratio **3 : 1**,† so that the 2-carboxyl substituent should have a bathochromic shift of **5—10** mμ.

Compound	$\lambda_{max.}$ (mμ) (solvent)	ε	Shift (mμ)	Ref.
(*A*) Me·CH:CH·CH:CH_2	223 (EtOH)	23,000	—	*a*
(*B*) Me·CH:CH·CH:CH·CO_2H	254 (EtOH)	26,000	31	*b*
(*C*) Cyclohexa-1,3-diene	256 (C_6H_{14})	8000	—	*c*
(*D*) 6-Methylcyclohexa-1,3-dienecarboxylic acid	283	—	27	*d*
(*E*) 4-Methylcyclohexa-4,6-diene-1,2-dicarboxylic acid	296 (EtOH)	8750	32 *	*e*
(*F*) 2,6,6-Trimethylcyclohexa-1,3-dienecarboxylic acid	291	—	32 †	*d*
(*G*) Cyclohexa-1,3-diene-1,4-dicarboxylic acid	309 (EtOH)	27,300	27 ‡	*f*
(*H*) 5-Methylcyclohexa-1,3-diene-1,3,5-tricarboxylic acid	291 (EtOH)	3080	30; 5 ¶	*g*

* Assumptions: the 1-methyl group contributes 7 mμ; [8] † the 2-methyl group contributes **3** mμ; [8] ‡ the shifts are additive; ¶ the 1-carboxyl group contributes **30** mμ, then the 2-carboxyl group contributes 5 mμ.

References: (*a*) Booker, Evans, and Gillam, *J.*, 1940, 1453. (*b*) Allan, Jones, and Whiting, *J.*, 1955, 1865. (*c*) Henri and Pickett, *J. Chem. Phys.*, 1939, **7**, 439. (*d*) Wendt, *Ber.*, 1941, **74***B*, 1242. (*e*) Hennion, Sheehan, and Maloney, *J. Amer. Chem. Soc.*, 1950, **72**, 3545. (*f*) Burnell and Taylor, *J.*, 1954, **3637**. (*g*) Prepared as described by Woolf and Heip, *Annalen*, 1899, **305**, 135.

Further confirmation of the structure of the monomeric ester was obtained from the spectrum of the maleic anhydride adduct. The adduct previously reported [2,11] was

* The substance is transparent in the **350—400** mμ region where simple fulvenes have a band of moderate intensity (ε **300**).[8] This fact excludes the fulvenoid structure (A).

† This ratio is correct for the methyl derivatives (**7** and **3** mμ respectively).[10]

[8] Bergmann, "Progress in Organic Chemistry," Vol. III, p. **103**, Butterworths Scientific Publications, London, 1955.

[9] Longuet-Higgins and Sowden, *J.*, 1952, **1404**; Coulson, *Proc. Phys. Soc.*, 1952, **65**, *A*, **933**; Peters, *J.*, 1957, **646**, 1993.

[10] Booker, Evans, and Gillam, *J.*, **1940**, **1453**.

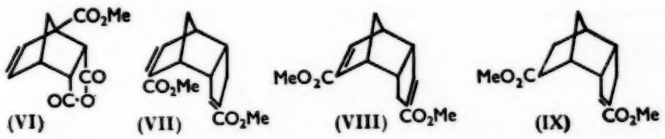
[11] Alder and Stein, *Annalen*, **1934**, **514**, 1.

precipitated in 40% yield from equimolar quantities in ether at room temperature. Examination of the mother-liquors for a second isomer gave only the dimeric ester in some 45% yield, showing that reconversion into the dimer competes with reaction with maleic anhydride. The spectrum of the adduct shows only ethylenic and carboxyl adsorption in the 220 mμ region, so the adduct is (VI), rather than the isomer from (II) or (IV).

Both the chemical and the spectroscopic evidence indicate that the monomer is methyl cyclopenta-1,3-dienecarboxylate (III).

Structure of the Dimeric Ester.—If structure (III) is accepted for the monomer, several reasonable structures can be written for the dimer. None of these is in agreement with the structure suggested by the following evidence.

The ultraviolet spectrum of the dimeric acid and ester (Fig. 2) shows intense adsorption in the 220 mμ region, an indication [12] that one or both of the carboxyl groups are conjugated with a double bond. In addition, there is a point of inflection in the 225—230 mμ region, which suggests that there are two chromophores which have similar but not identical adsorptions: if so, both carboxyl groups are conjugated with double bonds, giving a structure such as (VII) or (VIII). Day [13] reached the same conclusion. It was confirmed by catalytic hydrogenation to the known dihydro-compound, to be written as (IX) or its isomer from (VIII) since the double bond in the bicycloheptene ring is hydrogenated preferentially. The spectrum of this compound (Fig. 2, $\lambda_{max.}$ 228 mμ) shows that reduction has destroyed one, but not both, of the chromophores. If the second peak is resolved out of the spectrum of the dimeric ester, a single peak at 216 mμ remains. The tetrahydro-derivative shows only the carboxyl adsorption. We infer that the 216 mμ peak is due to the αβ-unsaturated carboxyl group in the bicycloheptene system, while the peak of lower intensity, at 228 mμ, is due to the αβ-unsaturated carboxyl group in the cyclopentene ring. Confirmation is provided by the spectrum of compound (V) and its dihydro-derivative, which show only the 228 mμ peak.



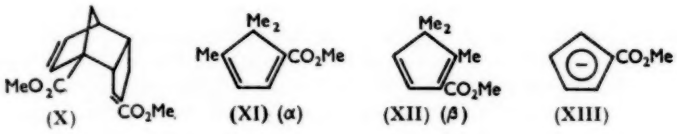
Additional evidence was obtained from oxidation of the dimeric ester with perbenzoic acid. It is known [14] that both double bonds in di(cyclopentadiene) are epoxidised at the same rate: treatment of the dimeric ester with two equivalents of perbenzoic acid led to very slow oxidation of *both* double bonds. It is known [15] that αβ-unsaturated carboxyl groups are oxidised relatively slowly, so we conclude again that both double bonds carry carboxyl groups.

It is clear that if structures (III) and (VII) are accepted, the depolymerisation and polymerisation are not simple reactions. It has now been shown that the former is straightforward, the monomeric ester being obtained in some 90% yield, but that the latter reaction is complex. The dimeric ester is contaminated with an oil, and chromatography gave a small quantity of a second dimer, whose ultraviolet spectrum (Fig. 2) shows that only the carboxyl group in the cyclopentene ring is conjugated with a double bond. This isomer has formula (X), the dimer which is readily obtained from two molecules of (III). Weise [16] isolated an *exo*-isomer of the dimer of cyclopentadienecarboxylic acid which is not identical with the present isomer. The spectrum of the original oil shows that some 20% of this material is formed in the dimerisation.

[12] Nielsen, *J. Org. Chem.*, 1957, **22**, 1539; Jones, Mansfield, and Whiting, *J.*, 1956, 4073.
[13] Day, *Diss. Abs.*, 1958, **19**, 39.
[14] Alder and Stein, *Annalen*, 1931, **485**, 223.
[15] Swern, *J. Amer. Chem. Soc.*, 1947, **69**, 1692.
[16] Weise, U.S.P., 2,781,395.

It is now clear that a hydrogen shift occurs in the dimerisation and in the depolymerisation. A possible explanation is that (III) and (IV) are in reversible thermodynamic equilibrium. Isomer (III) would be expected to predominate under normal conditions since the π-electron energy of the straight-chain system should be greater than that of the cross-conjugated system. As a diene in the Diels–Alder reaction, however, isomer (IV) should be more reactive since conjugation is preserved in the product and presumably in the transition state: Braude and Evans [17] have shown that butadienyl systems with 2-carboxyl groups are very good dienes in the Diels–Alder reaction. The effect of this situation is to cause most, but not all, of the dimerisation to occur with one molecule each of (III) and (IV) to give the dimer (VII).

The postulated rearrangement has a close precedent in the α- and β-camphylic acids (XI, XII),[18] which are interconvertible,[19] with the α as the more stable, and it is tempting to postulate that the driving force for the rearrangement is provided by the partial development of the stable cyclopentadienyl anion in the transition state. In other words, the anion (XIII) is a major contributor to the valence-bond wave function of the transition state.



(X) (XI) (α) (XII) (β) (XIII)

One difficulty remains. Maleic anhydride reacts with the monomeric ester to give a compound derived from (III), not from (IV). Our supposition that equilibration of (III) and (IV) leads to diene reaction through the latter form is only partly true since some dimer from two molecules of (III) is formed and it seems that the rates of several reactions are quite similar, so that detailed kinetic studies would be required before a firm decision could be made.

Experimental

Ultraviolet spectra refer to absolute ethanol solutions in a Hilger Uvispek spectrophotometer. Raney nickel was prepared as described by Paul and Hilly.[20]

Thiele's Dimeric Acid.—Cyclopentadienylmagnesium bromide (4 moles) in dry ether (2·5 l.) was prepared by refluxing ethylmagnesium bromide (4 moles) with cyclopentadiene (4·2 moles) until evolution of ethane ceased (12 hr.). Dry carbon dioxide was passed into the clear dark solution for 2 hr., after which a thick green oil had separated, leaving a clear yellow ethereal layer. Water, followed by dilute sulphuric acid, was added, the ether layer not reacting and the oil reacting vigorously. Stirring was continued until two clear layers containing a suspended solid were obtained. After filtration, the precipitate was taken up in aqueous ammonia, and after filtration was reprecipitated with acid, to give Thiele's dimeric acid (28%), m. p. 197—199°. Crystallisation from methanol (charcoal) gave material of m. p. 208° (lit.,[1a] 212°), $\lambda_{max.}$ 220 mμ (log ε 4·2). The aqueous layers were extracted with chloroform, and the combined organic layers extracted with sodium carbonate solution. Acidification of the aqueous extracts gave a further 0·2 mole of Thiele's acid contaminated with a brown impurity and 49 g. of a water-insoluble oil. Extraction of the acidified aqueous layers gave a water-soluble yellow acid (17 g.) which evolved carbon dioxide in boiling water, precipitating Thiele's acid.

The acid (60 g.) and concentrated sulphuric acid (50 c.c.) were refluxed in methanol (1 l.) for 12 hr. The acid was neutralised, the solvent evaporated, and water added, to give a white ester which, crystallised from light petroleum (b. p. 60—80°), had m. p. 85° (lit.,[1a] 85°) (50·5 g.,

[17] Braude and Evans, *J.*, 1956, 3238.
[18] Lewis and Simonsen, *J.*, 1936, 734; 1937, 457.
[19] Alder and Windemuth, *Annalen*, 1939, **543**, 28.
[20] Paul and Hilly, "Newer Methods of Organic Chemistry," Interscience Publ. Inc., New York, 1948, p. 65.

75%) [Found: C, 67·8; H, 6·9; *M* (Rast), 209, (cryoscopic in H_2O), 241. Calc. for $C_{14}H_{16}O_4$: C, 67·7; H, 6·5; *M*, 248], $\lambda_{max.}$ 220 mμ (log ε 4·2). This compound does not decolorise bromine in carbon tetrachloride, but decolorises potassium permanganate in acetone immediately.

The Monomeric Ester and the Second Dimer.—Thiele's ester (12 g.) was distilled into a receiver at −70° (b. p. 110—120°/14 mm.), giving crystals (10·9 g.), $\lambda_{max.}$ 274 mμ (log ε 3·71). Cyclopentadiene under the same conditions had $\lambda_{max.}$ 238 mμ (log ε 3·62). On warming to room temperature, the white solid first melted and then resolidified exothermally, to a white wax, in a few minutes. Crystallisation from light petroleum (b. p. 60—80°) gave Thiele's ester (5·2 g.): the mother-liquors gave an oil (5·0 g.) which was chromatographed on silica gel. Elution with 1% of ether in light petroleum (b. p. 40—60°) gave the second isomer (0·35 g.), m. p. 103—104° [from light petroleum (b. p. <40°)] [Found: C, 67·6; H, 6·4%; *M* (Rast), 188, (cryoscopic in benzene), 277], $\lambda_{max.}$ 230 mμ (log ε 3·81).

Hydrogenation of Methyl Cyclopentadienecarboxylate.—Thiele's ester (5·0 g.) was distilled at 10 mm. into a cold receiver, and the distillate (4·4 g.) hydrogenated in ethanol (100 c.c.) over Raney nickel at atmospheric pressure until uptake ceased (1200 c.c.; $2H_2$, 1570 c.c.). Distillation of the product gave methyl cyclopentanecarboxylate (0·9 g.), b. p. 142—146°. Hydrolysis with refluxing aqueous sodium hydroxide gave cyclopentanecarboxylic acid whose *p*-bromophenacyl ester had m. p. 75° (lit.,[21] m. p. 75—76°) alone or mixed with a specimen prepared by carboxylating the Grignard derivative from cyclopentyl bromide (Found: C, 53·8; H, 5·1; Br, 24·7. Calc. for $C_{14}H_{15}O_3Br$: C, 54·0; H, 4·8; Br, 25·7%).

Hydrogenation of Thiele's Ester to the Dihydro- and the Tetrahydro-derivative.—The ester (2·0 g.) was hydrogenated in ethanol with freshly prepared Raney nickel at atmospheric pressure. There was a rapid uptake of hydrogen for 2 hr. (250 c.c.; $1H_2$, 220 c.c.), then the rate fell sharply. Filtration and evaporation gave the *dihydro-ester*, m. p. 88° [from light petroleum (b. p. 60—80°; charcoal)] (Found: C, 67·2; H, 7·8. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·25%), $\lambda_{max.}$ 228 mμ (log ε 3·76). The m. p. was depressed on admixture of the compound with Thiele's ester. The dihydro-ester decolorised potassium permanganate in acetone immediately. Hydrogenation for 16 hr. under the same conditions gave the tetrahydro-derivative, m. p. 77—78° (Found: C, 66·4; H, 8·1. $C_{14}H_{20}O_4$ requires C, 66·6; H, 8·0%), log ε_{220} 2·21. This compound also depressed the m. p. of Thiele's ester but a mixture with the dihydro-derivative had m. p. 80—82°. This compound does not decolorise potassium permanganate in acetone.

Maleic Anhydride Derivative of Methyl Cyclopentadienecarboxylate.—The distilled cyclopentadiene ester (4·4 g.) was taken up in dry ether containing maleic anhydride (3·2 g.). The adduct crystallised from the solution in 2 hr. It (3·1 g., 40%) had m. p. 150° (lit.,[11] 151—152°) log ε_{220} 2·30. The mother-liquors were evaporated to an oil (4·5 g.) which was chromatographed on silica gel. Elution with 15% of ether in light petroleum (b. p. 40—60°) gave Thiele's ester (0·9 g.) contaminated with an oil (1·0 g.). Elution with pure ether gave maleic acid, m. p. and mixed m. p. 136—137° (1·65 g.).

Methyl Tricyclo[5,2,$0^{2,6}$]*deca-3,8-diene- and -3-ene-carboxylate.*—These compounds were prepared as described by Alder *et al.*[3] Compound (V) had $\lambda_{max.}$ 230 mμ (log ε 3·83); the monoene had $\lambda_{max.}$ 230 mμ (log ε 3·82). Compound (V) decolorised bromine in carbon tetrachloride immediately; the monoene did not. Both compounds decolorised potassium permanganate in acetone immediately.

Epoxidation of Thiele's Ester.—Di(cyclopentadiene) (0·0033 mole) and perbenzoic acid (0·0066 mole) in chloroform (10 c.c.) reacted exothermally at 0°. Titration after 30 min. showed that 96% of the oxidant had been consumed. Thiele's ester under the same conditions consumed 20% of the total oxidant in 16 hr.

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[21] Mitsui and Inagaki, *J. Agric. Chem. Soc. Japan*, 1951, **25**, 63; *Chem. Abs.*, 1953, **47**, 9303*f*.

XUM

351. *Nucleophilic Displacements in Organic Sulphites. Part V.* The Acid-catalysed Hydrolysis of Diethyl Sulphite and of Dimethyl Sulphite.*

By C. A. Bunton, P. B. D. de la Mare, and J. G. Tillett.

The hydrolyses of diethyl sulphite and dimethyl sulphite have been studied in aqueous solutions of mineral acids. They are considered to be of the concentration-dependent type of acid-catalysed reaction, with a superposed salt effect. Nucleophilic anions catalyse the reaction. The rates of the chloride-ion-catalysed reaction follow more closely Hammett's acidity function than the stoicheiometric acid concentration. By the use of oxygen-18, sulphur–oxygen bond-fission was found for both these compounds. The results are compared with those obtained earlier for the cyclic sulphites. The general applicability of the Zucker–Hammett hypothesis is discussed.

In Part II [1] it was shown that the hydrolyses of cyclic sulphites are catalysed by mineral acids. The variation of the rate with concentration of acid and the dependence of the rate on added salts were examined. The present paper provides similar data for two dialkyl sulphites, thus enabling a comparison to be made between the cyclic and open-chain systems.

Experimental

Dialkyl sulphites were prepared by the standard method.[2] Diethyl sulphite had b. p. 158°/760 mm., n_D^{25} 1·4130; dimethyl sulphite, b. p. 126°/760 mm., n_D^{25} 1·4070. The infrared spectrum of diethyl sulphite, determined by using a Grubb-Parsons double-beam infrared spectrometer in the range 700—3100 cm.$^{-1}$, had absorption bands at 714, 743, 813, 877, 894, 1000, 1010, 1093, 1157, 1208, 1289, 1393, 1451, 1479, 1623, and 3030 cm.$^{-1}$.

Position of Bond-fission.—Hydrolysis in acid solution. Diethyl sulphite (*ca.* 16 g.) was added to water enriched with ^{18}O (100 ml.) and perchloric acid (3·0M) and kept for 12 hr. at room temperature. The resulting solution was neutralised (phenolphthalein) and fractionated through a 20 × 1½ cm. column packed with glass helices. The fraction of b. p. 78—80° was collected and dried ($MgSO_4$). After redistillation the sample of b. p. 75—75·5°, n_D^{25} 1·3630, was used for isotopic analysis. A similar procedure was used for dimethyl sulphite.

Isotope analysis. The alcohol was pyrolysed to carbon monoxide on red-hot carbon at low pressure in a radiofrequency heater. The carbon monoxide was analysed mass-spectrometrically. The following values (atoms % excess of ^{18}O) were obtained. Dimethyl sulphite: water (solvent) 0·325, alcohol 0·008; diethyl sulphite: water (solvent) 0·453, alcohol 0·034.

Absence of ethyl chloride from the hydrochloric acid-catalysed hydrolysis of diethyl sulphite. Diethyl sulphite (0·88M) was hydrolysed in 100 ml. of aqueous hydrochloric acid (3M). When reaction was complete, nitrogen was bubbled through the solution to displace any ethyl chloride (which would not have been hydrolysed under the mild conditions needed for decomposition of the sulphite). Chloride ion was then determined. A blank solution, from which sulphite had been omitted, was treated similarly. No significant difference in concentration of chloride ion was observed, so no significant quantity of ethyl chloride had been produced.

Acid-catalysed hydrolyses. The acids were of Analytical Reagent quality. Their concentrations were determined by titration with standard alkali. Sodium chloride, sodium bromide, and sodium perchlorate were dried at 120°; the latter was free from halide. Sodium toluene-*p*-sulphonate was a commercial recrystallised specimen.

The rates of hydrolysis at 35° and above were determined by a conventional sealed-tube method. The conversion of organic sulphite into sulphur dioxide was determined at intervals by breaking samples under excess of standard iodine solution, which was then back-titrated with sodium thiosulphate. The runs at 0° and 25° were carried out in stoppered flasks. Aliquot portions (usually 5·0 ml.) were withdrawn at intervals and quenched in a large excess (200 ml.) of ice-cold water containing excess of iodine which was then back-titrated as above.

* Parts I—IV, *J.*, 1958, 4751, 4754, 4761, 4766.

[1] Bunton, de la Mare, and Tillett, *J.*, 1958, 4754.

[2] Voss and Blanke, *Annalen*, 1931, **485**, 273.

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The following exemplifies a typical kinetic run for 0·033M-diethyl sulphite in 0·270M-perchloric acid at 35·0°.

Time (min.)	0	5	10	15	20	25	
Titre (ml. of 0·0100N-iodine)	6·48	8·35	10·27	12·25	13·98	14·95	
10^4k_1 (min.$^{-1}$)	—	1·75	1·68	1·79	1·78	1·70	
Time (min.)	30	40	50	60	90	120	∞
Titre (ml. of 0·0100N-iodine)	16·15	18·66	20·26	22·29	25·17	27·91	30·99
10^4k_1 (min.$^{-1}$)	1·67	1·72	1·65	1·73	1·60	1·73	—

The finite titre for time (t) = 0 represents reaction during the time allowed for warming the samples to the temperature of the thermostat. Values of k_1 have been calculated by the use of the formula $k_1 = 2{\cdot}303 \log_{10}\{a/(a-x)\}/t$, where a is the molarity of organic sulphite at time (t) = 0 and x is the molarity of sulphur dioxide liberated at time t. The fact that the first-order rate-coefficients calculated by the use of the above formula are substantially constant over considerably more than 50% of reaction implies that one mole of material titrating as sulphur dioxide is liberated for each mole of organic sulphite decomposed.

The results are summarised in the Tables. Values of H_0 are included for reference, and mostly are taken from Long and Paul's review.[3]

TABLE 1. *First-order rate-coefficients and related data for the hydrolysis of diethyl sulphite in water.*

(a) At 0·0°.						
[$HClO_4$] (M)	0·50	1·03 *	2·06	3·09	3·61	4·12
10^3k_1 (min.$^{-1}$)	0·50	1·22	2·76	5·14	8·92	13·4
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	1·00	1·19	1·34	1·66	2·47	3·26
H_0	0·31	−0·25	−0·80	−1·28	−1·53	−1·78
[$HClO_4$] (M)	4·64	5·15	5·67	6·18	6·70	7·21
10^3k_1 (min.$^{-1}$)	20·7	27·7	51·1	69·6	135	265
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	4·47	5·38	9·02	11·2	20·1	37·8
H_0	−2·05	−2·32	−2·65	−2·98	−3·36	−3·76
(b) At 0·0°, with added sodium perchlorate.						
[$HClO_4$] (M)	0·000	1·000 *	2·000	3·000	4·000	5·000
[$NaClO_4$] (M)	6·000	5·000	4·000	3·000	2·000	1·000
10^3k_1 (min.$^{-1}$)	0·00	3·29	8·05	14·8	24·9	41·9
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	—	3·29	4·03	4·93	6·23	8·38
H_0	—	−1·46	−1·84	−2·13	−2·47	−2·77
[$HClO_4$] (M)	6·000	0·000	1·000 *	2·000	3·000	4·000
[$NaClO_4$] (M)	0·000	4·000	3·000	2·000	1·000	0·000
10^3k_1 (min.$^{-1}$)	60·0	0·00	1·99	4·24	7·97	13·4
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	10·0	—	1·99	2·12	2·66	3·35
H_0	−3·05					
(c) At 0·0°, with hydrochloric acid.						
[HCl] (M)	1·000	1·500	2·000	3·000	4·000	
10^3k_1 (min.$^{-1}$)	3·95	9·99	21·6	76·2	246	
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	3·95	6·66	10·8	25·4	61·5	
H_0	−0·20	−0·47	−0·69	−1·05	−1·40	
(d) At 0·0°, with 0·25M-sodium chloride and added sodium perchlorate.						
[$HClO_4$] (M)	1·03	2·06	3·09	4·12	5·15	5·67
[$NaClO_4$] (M)	0·000	0·000	0·000	0·000	0·000	0·000
10^3k_1 (min.$^{-1}$)	1·92	6·04	16·9	51·0	185	328
H_0 †	−0·25	−0·80	−1·28	−1·78	−2·32	−2·65
$4 + \log_{10} \Delta k_1$ ‡	0·898	1·516	2·072	2·575	3·196	3·443
[$HClO_4$] (M)	6·18	1·000	2·000	3·000		
[$NaClO_4$] (M)	0·000	5·000	4·000	3·000		
10^3k_1 (min.$^{-1}$)	566	14·9	41·8	83·8		
H_0 †	−2·98	−1·46	−1·84	−2·13		
$4 + \log_{10} \Delta k_1$ ‡	3·696	2·065	2·529	2·839		
(e) At 0·0°, with hydrochloric acid and added sodium chloride.						
[HCl] (M)	1·000	2·000	3·000	4·000		
[NaCl] (M)	3·000	2·000	1·000	0·000		
10^3k_1 (min.$^{-1}$)	35·4	84·6	164	246		
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	35·4	42·3	54·6	61·5		

[3] Long and Paul, *Chem. Rev.*, 1957, **57**, 1.

TABLE 1. (*Continued.*)

(*f*) *At* 0·0°, *with added sodium chloride.*

$[HClO_4]$ (M)	1·03	1·03	2·06	2·06	3·09	3·09	4·12	5·15	5·15
[NaCl] (M)	0·500	1·000	0·500	1·000	0·500	1·000	0·500	0·100	0·200
10^3k_1 (min.$^{-1}$)	3·34	5·84	10·6	20·9	32·2	61·2	90·9	92·0	142

(*g*) *At* 35·0°.

$[HClO_4]$ (M)	0·000	0·103	0·270	0·412	0·540	1·08	1·500	2·060
10^3k_1 (min.$^{-1}$)	0·000	6·7	17·1	27·5	38·5	104	111	176
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	—	65·2	63·2	66·7	71·2	96·5	74·0	85·5

(*h*) *At* 35·0° *with* 0·270M-*perchloric acid.*

$[NaClO_4]$ (M)	0·000	1·000	2·000	3·000
10^3k_1 (min.$^{-1}$)	17·1	21·8	27·6	34·9
[NaCl] (M)	0·000	0·100	0·200	0·300
10^3k_1 (min.$^{-1}$)	17·1	23·0	29·8	34·9
[NaBr] (M)	0·000	0·030	0·100	0·200
10^3k_1 (min.$^{-1}$)	17·1	19·7	30·0	38·7
$[C_7H_7\cdot SO_3Na]$ (M)	0·000	0·500	1·000	1·500
10^3k_1 (min.$^{-1}$)	17·1	20·0	20·5	21·5

(*i*) *At* 24·9°.

$[HClO_4]$ (M)	1·03	2·06	3·09	4·12
10^3k_1 (min.$^{-1}$)	20·8	55·9	123	250
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	20·2	27·2	39·8	60·8
H_0	−0·25	−0·80	−1·28	−1·78

For 0·27M-$HClO_4$ at 50°, $10^3k_1 = 85·0$; for 0·03M-$HClO_4$ at 73·0°, $10^3k_1 = 78·4$.

* See text.
† In absence of added chloride ions.
‡ $\Delta k_1 = k_1$ in presence of chloride $- k_1$ in absence of chloride, under otherwise identical conditions.

TABLE 2. *First-order rate-coefficients for the hydrolysis of dimethyl sulphite in water.*

(*a*) *At* 0·0°.

$[HClO_4]$ (M)	2·06	3·09	4·12	5·15	6·18	7·21
10^3k_1 (min.$^{-1}$)	1·22	2·29	7·78	13·5	30·0	73·5
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	0·59	0·74	1·89	2·61	4·85	10·2
H_0	−0·80	−1·28	−1·78	−2·32	−2·98	−3·76

(*b*) *At* 0·0° *with added sodium perchlorate.*

$[HClO_4]$ (M)	1·000	3·000	4·000	5·000	6·000
$[NaClO_4]$ (M)	5·000	3·000	2·000	1·000	0·000
10^3k_1 (min.$^{-1}$)	1·62	8·33	12·6	16·5	27·5
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	1·62	2·78	3·15	3·30	4·50
H_0	−1·46	−2·13	−2·47	−2·77	−3·05

(*c*) *At* 0·0°, *with hydrochloric acid.*

[HCl] (M)	2·000	3·000	4·000
10^3k_1 (min.$^{-1}$)	8·08	21·9	82·6
$10^3k_1/[H^+]$ (l. mole^{-1} min.$^{-1}$)	4·04	7·30	20·65
H_0	−0·69	−1·05	−1·40

Influence of temperature. The entropy (ΔS^*) and the energy of activation (ΔE), calculated by using the formula $k = (ekT/h) \exp(\Delta S^*/R) \exp(-\Delta E/RT)$ for diethyl sulphite in 1M-perchloric acid are $\Delta S^* = -8·2$ e.u. and $\Delta E = 20·3$ kcal. mole^{-1}. The entropies of activation found for ethylene and trimethylene sulphites [1] were respectively −15·8 e.u. and −13·0 e.u., so the value now found for diethyl sulphite is significantly less negative; the activation energy is correspondingly slightly higher.

Long, Pritchard, and Stafford [4] have recently elaborated Taft's earlier suggestion [5] that Hammett-dependent and concentration-dependent reactions within the same class of compound should differ in entropy of activation (ΔS^*) by some 20—30 e.u. Typical values for unimolecular (*A*1) and bimolecular (*A*2) acid-catalysed hydrolyses of carboxylic esters are

[4] Long, Pritchard, and Stafford, *J. Amer. Chem. Soc.*, 1957, **79**, 2362.
[5] Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 5372.

+5 and −20 e.u. respectively; but there is no certainty that other classes of ester would have these typical values.*

On this criterion, the hydrolyses of cyclic and non-cyclic sulphites do not differ greatly, but both lie intermediate between values characteristic of typical reactions of the two classes of carboxylic ester. A definite answer concerning the presence or absence of a water molecule in the rate-determining stage is therefore not yet given by the data on entropies of activation for hydrolysis of organic sulphites, but it is considered that the negative values obtained are not inconsistent with the bimolecular mechanism proposed for the cyclic sulphites.

Position of bond-fission. Hydrolysis of dimethyl or diethyl sulphite in water enriched in ^{18}O gives essentially normal alcohol. The slight enrichment recorded for the hydrolysis of diethyl sulphite is probably caused by incomplete drying of the sample, and we consider that entire sulphur–oxygen bond-fission has occurred.

Discussion

Kinetic Form.—The kinetic forms observed for diethyl and dimethyl sulphite are very similar. A more extensive examination has, however, been made of diethyl sulphite, and the illustrations for the discussions will be taken from data on this compound.

Many acid-catalysed reactions fall into one of two classes, according to whether the logarithm of the first-order rate-coefficient increases linearly with the logarithm of the stoicheiometric acidity or with Hammett's acidity function, H_0. This criterion has been used widely in the study of acid-catalysed reactions, and evidence obtained by its use has, in general, been in accord with expectations derived from other data. The terms concentration-dependent and Hammett-dependent will be used to describe the two types of mechanism.

Ethylene and trimethylene sulphites undergo acid-catalysed hydrolysis; the reactions behave kinetically in a way which at first sight is intermediate between the above classes. From consideration of the detailed effects of nucleophilic anions as catalysts, in conjunction with studies of the position of bond-fission, it was concluded that the hydrolyses of these sulphites fall into the concentration-dependent class, with a superposed increase in the rate of reaction when the concentration of electrolyte in the medium is increased, as it is by increase in concentration of acid.

The behaviour of the open-chain sulphites is generally very similar, but there are significant differences which require special comment.

Correlation of rate with acidity. In Fig. 1 are plotted the logarithms of the rate of hydrolysis of diethyl sulphite against values [3] of Hammett's acidity function. The reaction had been followed well into the region of acidity in which h_0 and $[HClO_4]$ are markedly different.

Considering first only the effects of variation in the concentration of perchloric acid, the values lie near to a straight line of slope 0·69. In contrast with the results obtained previously for ethylene sulphite, there is no curvature at the highest acidities. A Hammett-dependent reaction would give a straight line of unit slope, although appreciable deviations from such ideal behaviour have been observed for reactions which are accepted as falling into this class.[3]

A low Hammett slope for an acid-catalysed reaction might arise from a bimolecular reaction which has a high positive salt effect (cf. the hydrolysis of ethylidene diacetate [6]), or from a unimolecular reaction which has a negative salt effect, *i.e.*, from a unimolecular reaction in which conditions are such that the activity-coefficient equality, $f_S/f_{X^+} = f_B/f_{BH^+}$, which is one of the main conditions for a unit slope, does not hold.

It seems necessary, therefore, to use some further criterion to decide whether or not the reaction is Hammett-dependent. The addition of sodium perchlorate to solutions of

* Thus the characteristic value for the unimolecular acid-catalysed ring opening of epoxides [4] is −5 e.u.

[6] Bell and Lukianenko, *J.*, 1957, 1687.

perchloric acid increases the acidity of the solution as measured by H_0.[3] As for the cyclic sulphites, however, the rates of the acid-catalysed hydrolysis of diethyl sulphite are not increased to the same extent. This is shown in Fig. 1; the triangles refer to experiments in which sodium perchlorate has been added to perchloric acid to make the total concentration of perchlorate ion 6·0M.

The above results, considered as a whole, suggest that the reaction is not Hammett-dependent. Neither, however, is the rate directly proportional to the stoicheiometric concentration of acid. This is illustrated by the values given in Tables 1(*a*), 1(*b*), 1(*g*), 1(*h*), 1(*i*), 2(*a*), and 2(*b*). The values of $k_1/[H^+]$ rise quite considerably, and vary twenty-fold over a range of concentration of perchloric acid 0·5—6·7M.

When the reaction is carried out with the perchlorate-ion concentration kept constant by addition of sodium perchlorate, the rate is proportional to the concentration of perchloric

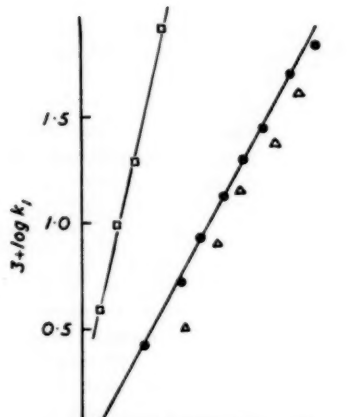


FIG. 1. *Hammett plot for the acid hydrolysis of diethyl sulphite at 0°.*

● $HClO_4$
△ $HClO_4 + NaClO_4$
□ HCl

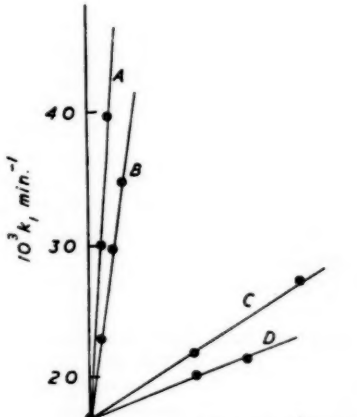


FIG. 2. *Effect of added salts on the acid hydrolysis* (35·0°, 0·27M-$HClO_4$).

A, NaBr.
B, NaCl.
C, $NaClO_4$.
D, $C_7H_7 \cdot SO_3Na$.

acid only below about 2·0M; above this concentration, considerable deviations occur, and the plot takes the form of an upward curve; in this, the behaviour differs from that of ethylene sulphite.

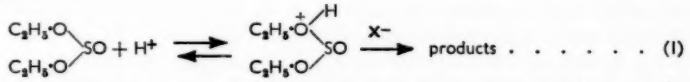
Effects of nucleophilic anions and other added salts on the rate of hydrolysis. In Fig. 1 are shown also points corresponding to the use of hydrochloric acid. These fall on a straight line which lies well above the curve obtained for perchloric acid. The difference in rates can be judged from the values shown in Table 1(*c*).

In Fig. 2 are shown the points corresponding to the effects of added salts on the reaction at low acidity. As for hydrolysis of ethylene sulphite, the salts fall into two well-defined classes. The first includes sodium perchlorate and sodium toluene-*p*-sulphonate, for which the overall effect is small. The second includes sodium chloride and sodium bromide. These have a very marked catalytic effect, and the rate is proportional to the concentration of salt.

This enhanced catalytic power, shown by salts in the latter class, seems to be associated

with the anion, and we believe that this is another example of specific catalysis by anions. The effects of the negative ions concerned are in order of their nucleophilic power, *i.e.*, $Br^- > Cl^-$. It seems reasonable, therefore, to attribute this type of catalysis to nucleophilic attack by the negative ion on the sulphur atom of the conjugate acid, as was found also for the cyclic sulphites.

Mechanism.—The acid-catalysed aqueous hydrolysis of esters usually involves a pre-equilibrium non-rate-determining proton-transfer to form the conjugate acid, as in the first step of sequence (1). The proton might be associated with either of the two different types of oxygen atoms.



(1)

Both for the cyclic sulphites and for the non-cyclic sulphites, hydrolysis could in principle proceed either by the bimolecular ($A2$) mechanism (sequence 1) in which a water molecule participates covalently in the rate-determining attack on sulphur, or by the $A1$ mechanism, in which the second stage is unimolecular, followed by a non-rate-determining process. The present hydrolysis gives behaviour intermediate between these two as judged by (*a*) by the Zucker–Hammett criterion, (*b*) the effects of added salts, (*c*) the entropy of activation. Three interpretations are possible, *viz.*: (i) that the reaction falls into one or other of the two classes, and therefore that the criteria are not satisfactory for mechanistic diagnosis in this case; (ii) that the two mechanisms proceed concurrently, making similar contributions to the rate; and (iii) that the reaction in some ill-defined way can be regarded as of intermediate mechanism. Interpretation (ii) would imply that the contributions from the two mechanisms would change with structure and with conditions, as in the hydrolysis of diphenylmethyl trifluoroacetate [7] in aqueous dioxan, where the contributions of mechanism $A_{Ac}2$ and $A_{Al}1$ can be changed by change in acidity or temperature. No indication of such a change has been found in the present results. It has been pointed out that, when a single molecular encounter leading to reaction is considered, interpretation (iii) involves difficulties [8] which seem to us to be associated with the problem of differentiating between covalent and electrostatic interactions in the transition state. In the present discussion, therefore, interpretation (i) has been adopted; so, by analogy with the halide-catalysed reaction, discussed below, and in accordance with our treatment of the cyclic sulphites, the bimolecular mechanism is considered to be the most probable. This is the basis of the following discussion (cf. ref. 9).

Environmental Effects.—For a concentration-dependent hydrolysis of the type shown in equation (1), the Brönsted equation takes the form: [3]

$$\text{Rate} = k[S][H^+] \cdot f_S a_w \cdot f_{H^+}/f^{\ddagger} \quad (2)$$

Here $f^{\ddagger}$ is the activity coefficient of the transition state, which contains the substrate (S), water, and a proton; a_w is the activity of water; the other symbols have their customary meaning.

In some examples of reactions considered to follow this path, the activity coefficient ratio $f_S a_w f_{H^+}/f^{\ddagger}$, is near to unity in the critical experimental region, and hence the rate of reaction is a linear function of the stoicheiometric concentration of acid, as is required by the Zucker–Hammett hypothesis. Such a limiting situation is not achieved in the present case, and many other examples of such deviations from ideal behaviour have been found. Thus, the rate of hydrolysis of ethylidene diacetate [6] is not accurately proportional to the acid concentration, the deviation increasing with increasing acid-strength. Similarly, the rates of hydrolysis of methyl formate and ethyl acetate,[10] of methyl

[7] Bunton and Hadwick, unpublished result.
[8] Gold, *J.*, 1956, 4633.
[9] Bunton, de la Mare, Lennard, Llewellyn, Pearson, Pritchard, and Tillett, *J.*, 1958, 4761.
[10] Bell, Dowding, and Noble, *J.*, 1955, 3106.

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benzoate,[11] and of methyl phosphate [12] show this positive salt-effect with increasing ionic strength.

In the present experiments, it is found that the rate of hydrolysis increases much more rapidly than would be expected if the rate was linearly dependent on acid concentration. If sodium perchlorate is added to keep the total concentration of electrolyte constant at 6M, the rate of hydrolysis still increases with acidity more rapidly than required for a linear relation when the concentration of perchloric acid is greater than about 2M. Hence, even in these mixtures the above activity-coefficient term is still not constant.

Since the salt-effects observed for diethyl and dimethyl sulphites are very similar, the size of the ester molecule does not seem to be critically important in determining the magnitude of the observed changes.

The following values are for the reaction catalysed by perchloric acid at constant concentration (1·03 ≃ 1·0M) in the presence of various amounts of added sodium perchlorate; they are taken from Tables 1(*a*) and 1(*b*), marked (*):

$[NaClO_4]$ (M) (and μ)	0 (1·0)	3·000 (4·0)	5·000 (6·0)
$3 + \log_{10} k_2$	0·079	0·299	0·517

There is an approximately linear relationship between $\log_{10} k_2$ and μ, the ionic strength. Bell [13] has pointed out that such a " linear salt-effect," varying with the nature of the electrolyte, can be justified in terms of the extension of the Debye–Hückel theory in which a term proportional to the ionic strength is included in the expression for the logarithm of the activity coefficient of an electrolyte; this term involves an empirical parameter characteristic of the ions present in the solution. In the present investigation, the catalytic powers of the three electrolytes, sodium perchlorate, sodium toluene-*p*-sulphonate, and perchloric acid are rather similar, but if a wider range of electrolytes were examined it is probable that this would not be found to be general. For the hydrolysis of ethylene sulphite, tetraethylammonium perchlorate had very little catalytic power.

The Halide-catalysed Reaction.—This, at low acidities, takes the kinetic form: $-\mathrm{d[sulphite]}/\mathrm{d}t = k[\mathrm{sulphite}][\mathrm{H^+}][\mathrm{Halide^-}]$. Because of the substantial catalysis, which greatly exceeds that expected for a salt of a non-nucleophilic anion, it is considered that, as for the cyclic sulphites, this reaction involves bimolecular attack by halide ions on the protonated intermediate. Ethyl chloride is not produced in the chloride-catalysed hydrolysis of diethyl sulphite, so the nucleophilic attack is on the sulphur, rather than on the carbon atom.

To investigate the form of the dependence of rate on acidity in this process, the reaction has been studied at relatively high acidity, with chloride ions present in amount (0·25M) sufficient to increase the rate of reaction, but insufficient, it is considered,[cf.3] to alter differentially the values of H_0 for the solutions. In Table 1(*d*) are values for the reaction catalysed by 0·25M-sodium chloride at different acidities, it being assumed that the added chloride ions do not differentially affect the rate of attack by water on the protonated sulphite. Values of $\log_{10} \Delta k_1$ are shown diagrammatically in Fig. 3. Somewhat surprisingly, points representing behaviour when sodium perchlorate is also added lie closely on the straight line of slope 1·12 which fairly accurately represents the relationship between $\log_{10} \Delta k_1$ and H_0. The corresponding slope for ethylene sulphite was 0·82. Both these values are in the range which would normally be regarded as indicating a Hammett-dependent process.

Comparison of Hammett Slopes for Acid-catalysed Hydrolyses in the Presence and in the Absence of Chloride Ions.—The plot of $\log_{10} k_1$ against H_0 for the hydrolysis of ethylene sulphite has a slope of 0·68; this is increased to 0·82 in the presence of chloride ions. The corresponding values for diethyl sulphite are 0·69 and 1·12. The reasonable correlation of

[11] Chmiel and Long, *J. Amer. Chem. Soc.*, 1956, **78**, 3326.
[12] Bunton, Llewellyn, Oldham and Vernon, *J.*, 1958, 3574.
[13] Bell, " Acid-Base Catalysis," Oxford, 1941, Chapter II.

$\log_{10} k_1$ with H_0 for the reaction which at low acidities has the kinetic form $-\text{d[sulphite]}/\text{d}t = k\text{[sulphite][H}^+\text{][Cl}^-\text{]}$ carries with it the implication that the ratio $f_S f_{H^+} f_{Cl^-}/f^{\ddagger}_{(Cl^-)}$ follows the corresponding ratio for protonation of a neutral indicator, $f_B f_{H^+}/f_{BH^+}$. The overall charge on the transition state for the chloride-catalysed reaction is zero.

It could not have been predicted that the introduction of a chloride ion into the transition state would not change greatly the form of the dependence of rate on acidity from that expected for a unimolecular ($A1$) hydrolysis. It is perhaps not surprising, however, that when it is found that the ratio $f_S f_{H^+} f_{Cl^-}/f^{\ddagger}_{(Cl^-)}$ accords with that expected for a unimolecular rate-determining reaction, in which the corresponding ratio is $f_S f_{H^+}/f^{\ddagger}_{(No\,Cl^-,\,No\,H_2O)}$, it is found also that the ratio for the uncatalysed reaction involving water as the nucleophil is not too different. In the latter case, the corresponding ratio is $f_S f_H f_{H_2O}/f^{\ddagger}_{(H_2O)}$. It is interesting that the direction of the change in slope of the plot of rate against acidity, and thence the change in the activity-coefficient ratio, is such that it accords with the most naïve interpretation of the Zucker–Hammett criterion,

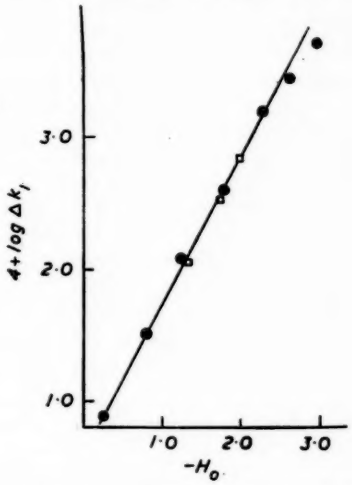

FIG. 3. *Hammett plot for the halide-catalysed acid hydrolysis.*

● $HClO_4$
□ $HClO_4 + NaClO_4$.

namely that a bimolecular reaction involving water as the reagent will become more nearly Hammett-dependent if some other nucleophilic agent takes the place of water in the rate-determining nucleophilic attack.

The present example so nearly approximates to behaviour characteristic of a Hammett-dependent reaction that it suggests the possibility that examples may in due course be found in which a bimolecular hydrolysis by water gives the behaviour of a Hammett-dependent reaction.[cf. 14]

Structural Effects: *Comparison of Open-chain and Cyclic Sulphites.*—The mechanisms of hydrolysis of these two groups of sulphites are, under our conditions, very similar. The rates of hydrolysis of the dialkyl sulphites are considerably greater than those of the cyclic sulphites. The relative rates, at 0°, in 1·0M-acid, are: ethylene sulphite,[1] 1; trimethylene sulphite,[1] 4; dimethyl sulphite, 20; diethyl sulphite, 48. This rate-difference is determined essentially by the difference in entropy of activation.

These results can be compared with those for the phosphate esters, which are the only other inorganic esters for which rate-data are available for both the cyclic and open-chain systems. In 1·0M-acid, ethylene phosphate hydrolyses about 10^6 times more rapidly than

[14] Deno and Perrizolo, *J. Amer. Chem. Soc.*, 1957, **79**, 1345; Taft, Deno, and Skell, *Ann. Rev. Phys. Chem.*, 1958, **9**, 303.

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dimethyl phosphate.[25] Similar results are obtained in alkaline solutions. Trimethylene phosphate, however, in 1·0M-alkali hydrolyses only slightly faster than dimethyl phosphate.

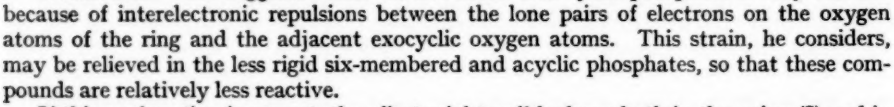
Thus the five-membered ring compound is very reactive in acid and alkaline solutions, but the reactivity of the six-membered phosphate is similar to that of the open-chain esters. This is not the case for the sulphites. Diethyl sulphite hydrolyses faster than either 1 : 2- or 1 : 3-cyclic sulphites in acid solution. The different reactivity sequences are not due simply to a different charge type of reaction, because the relative rates of hydrolysis are similar in the presence and the absence of halide ions, which specifically catalyse the reaction by attacking the sulphur atom of the protonated ester.

Differences may, however, occur in the basicity of the oxygen atoms. Clearly, under catalysis by acids, greater basicity will favour more protonation and thus increase the rate. The basicity of cyclic sulphoxides increases with ring size,[16] and so the increase in rate on going from ethylene to trimethylene sulphite might conceivably be explained if protonation were on the terminal oxygen atom and the basicities varied in a similar manner.

No data exist for the direct comparison of the basicities of cyclic and open-chain sulphites, but we do not suppose that the basicities would differ greatly, and certainly not sufficiently to cause the observed differences in rate.

Westheimer [15] has suggested that the five-membered cyclic phosphate is very reactive because of interelectronic repulsions between the lone pairs of electrons on the oxygen atoms of the ring and the adjacent exocyclic oxygen atoms. This strain, he considers, may be relieved in the less rigid six-membered and acyclic phosphates, so that these compounds are relatively less reactive.

If this explanation is correct, the effect might well be large both in the anion (I) and in the neutral molecule (II). In the protonated species (III), on the other hand, the positive charge would be expected, through its effect on the electronegativity of the oxygen atom, to reduce the size of the orbitals occupied by the adjacent lone-pairs of electrons, and might therefore reduce the differential effects of such interelectronic strains. It is not certain whether hydrolysis of (III) is rapid or not; the above theory fits the results for cyclic sulphites. For these compounds, the structural effects on the hydrolysis of the



(I) (II) (III) (IV) (V)

neutral species (IV) parallel those of the phosphates; ethylene sulphite is more reactive to alkali than is trimethylene sulphite. On the other hand, the conjugate acid (V) of ethylene sulphite shows no abnormal reactivity, as is consistent with the view that the lone-pair repulsions, responsible for the abnormally high reactivities of (I), (II), and (IV), disappear or are greatly reduced in (III) and (V).

We thank Professor E. D. Hughes, F.R.S., and Sir Christopher Ingold, F.R.S., for valuable discussion, and the Department of Scientific and Industrial Research for a Grant (to J. G. T.).

William Ramsay and Ralph Forster Laboratories,
University College, Gower St., London, W.C.1. [*Received, December 15th*, 1958.]

[15] Westheimer, Chem. Soc. Special Publ., No. 8, 1957, 1.
[16] Tamres and Searles, Abstracts of Papers, 131st Meeting, Amer. Chem. Soc., 1957, p. 10R.

352. *Studies on Transition-metal–Nitric Oxide Complexes. Part V.* Nitric Oxide Complexes of Tetrahedral Bivalent Nickel and Some Other Metals.*

By W. P. Griffith, J. Lewis, and G. Wilkinson.

Absorption spectra and magnetic susceptibility measurements have been made on the paramagnetic nitrosyl, hydroxy-, and alkoxy-complexes of nickel, and it is suggested that these contain bivalent, tetrahedral nickel. Studies have also been made on a similar complex of iron, and of the complexes $Rh^{-I}(NO)_2Cl$, $Pd^{0}(NO)_2Cl_2$, and $K[Co^{-I}(CN)(CO)_2NO]$.

This paper is concerned primarily with the paramagnetic nickel nitrosyl hydroxide, previously formulated as $Ni(NO)(OH)(H_2O)_2$, and the corresponding alkoxides. The present studies indicate that these complexes, which have been known for many years, must be formulated as containing tetrahedral bivalent nickel, for example, as $NiNO(OH)_3$, and it seems that they were the first compounds of this type to be prepared, although not recognised as such; other tetrahedral complexes of bivalent nickel have only recently been unambiguously proved.[1]

(1) *Nitric Oxide Hydroxy- and Alkoxy-complexes of Nickel.*—Shortly after the discovery of nickel tetracarbonyl, Berthelot [2] showed that nitric oxide reacted with the carbonyl in the vapour phase to give an ill-defined, blue, volatile product, to which the formula $Ni(NO)_2$ was later assigned by Mond and Wallis.[3] The complex and its " alcoholate " derivatives were studied later by Reihlen *et al.*,[4] by Frazer and Trout,[5] and, more intensively, by Anderson.[6,7] The present position is summarised by Emeléus and Anderson.[8]

Study of the nickel nitrosyl hydroxide is difficult owing to its extreme instability. According to Anderson,[7] the most representative formulation is $Ni(NO)(OH)(H_2O)_{1\cdot5}$ or $Ni(NO)(OH)(H_2O)_2$. It is prepared by passing nitric oxide into nickel carbonyl, either alone or in an inert solvent. Traces of water are necessary,[6] but too much water results in the formation of $Ni(OH)_2$; as a result of this, the yields of the reaction are very low. The complex dissolves in air-free water to a deep blue basic solution which decomposes within a few seconds; it is also soluble in alcohols, but not in benzene, chlorobenzene, nitrobenzene, or chloroform.

Anderson suggests [6,7] that the complex is $Ni(NO)(OH)(H_2O)_n$ ($n = 1$ or 2) containing univalent nickel. If this formula were correct, with NO donating as NO^+,[9] the nickel atom would formally be Ni^0, and the compound should be tetrahedral and diamagnetic, it being assumed to be monomeric. Anderson favoured univalent nickel since silver nitrate was apparently reduced. We have found that, in fact, silver oxide is formed owing to the basic nature of the solutions and not silver.

Magnetic measurements made over a temperature range (Table 1) show, however, that the complex has a moment of 2·97 B.M. with a large negative Curie temperature of −59°.

The infrared spectrum (Table 2) shows a strong peak at 1828 cm.$^{-1}$, typical of a co-ordinating NO^+ group.[9] There is also a strong OH peak near 3500 cm.$^{-1}$ but only weak

* Part IV, *J.*, 1959, 872.

[1] Venanzi, *J.*, 1958, 719.
[2] Berthelot, *Compt. rend.*, 1891, **112**, 1243.
[3] Mond and Wallis, *J.*, 1922, **121**, 33.
[4] (*a*) Reihlen, Gruhl, von Hessling, and Pfrengl, *Annalen*, 1930, **482**, 161; (*b*) Reihlen, *Z. anorg. Chem.*, 1937, **230**, 223.
[5] Frazer and Trout, *J. Amer. Chem. Soc.*, 1936, **58**, 2201.
[6] Anderson, Thesis, University of London, 1932.
[7] Anderson, *Z. anorg. Chem.*, 1936, **229**, 357.
[8] Emeléus and Anderson, " Modern Advances in Inorganic Chemistry," Routledge and Paul, London, 1952, p. 433.
[9] Lewis, Irving, and Wilkinson, *J. Inorg. Nuclear Chem.*, 1958, **7**, 32.

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absorption at 1630 cm.$^{-1}$; on Anderson's formulation strong absorption in the 1600 cm.$^{-1}$ region would be expected.

TABLE 1. *Magnetic measurements on* $Ni^{II}(NO)(OH)_3$ *(solid).*

T (°K)	297·5	265·5	248·0	227·5	204·0	168·0	135·5	114·5
χ_A (c.g.s.u. × 10^{-3})	3·08	3·46	3·65	3·82	4·23	4·91	5·65	6·06

Diamagnetic correction: -26×10^{-6} c.g.s.u.

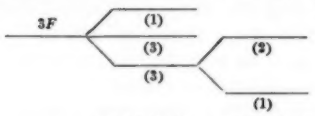
TABLE 2. *Infrared spectra.* (All in Nujol mulls.)

Compound	NO assigned frequency (cm.$^{-1}$)	Other strong bands (cm.$^{-1}$)
$Ni(NO)(OH)_3$	1828 (s)	3500
$Ni(NO)(OMe)_2OH$	1820 (s)	3500, 1030
$Ni(NO)(OEt)_2OH$	1820 (s)	3500, 1040
$Ni(NO)(OEt)(OH)_2$		
n-Propanol complex	1820 (s)	3500, 1050, 1010, 960
n-Butanol complex	1815 (s)	3500, 1240, 1050
$[Ni(NO_2)(OMe)(MeOH)]_2$	—	3500, 1410, 1270, 1030, 845
$Ni(NO_2)$-ethoxy-complex	—	3500, 1410, 1270, 1030, 845
$Fe_2(NO)_2(MeOH)_2(OMe)(OH)$	1752 (s)	3500, 1055, 1015
$Pd(NO)_2Cl_2$	1833 (s), 1818 (s)	—
$Rh(NO)_2Cl$	1703 (s), 1605 (s)	—
$K[Co(CN)(CO)_2(NO)]$	1720 (s)	2102, 2037, 1960

The methanolic solution of the hydroxy-complex (which will probably then exist as the methoxy-derivative described below) shows a strong absorption peak in the visible spectrum at 650 mμ, but no peak near 400 mμ.

The above facts lead to the conclusion that the complex contains either tetrahedral or octahedral bivalent nickel. Although it is not possible to obtain a molecular weight for either the nitrosyl hydroxide or the nitrosyl alkoxides, the blue colour of these species and the absence of a peak at 410 mμ are indicative of tetrahedral bivalent nickel complexes;[10] tetrahedral nickel complexes,[11,12] such as the $[NiCl_4]^-$ ion, are also known to absorb at 650 mμ.

The magnetic moment of the complex, 2·97 B.M., is in agreement with the value obtained by Venanzi [1] for the tetrahedral triphenylphosphinenickel derivatives, but is substantially lower than the value obtained by Nyholm *et al.*[12] for the tetrahalide derivatives of nickel. The ^3F state of nickel in a tetrahedral state will be split by a cubic crystalline field into two low-lying orbital triplets and a singlet level. This should then give rise to an appreciable orbital contribution, as found in the tetrahalides. If, however, a field of low symmetry is also present, the lowest triplet will be further split into a singlet and a doublet (see Figure). The orbital contribution can then be considerably reduced if the singlet–



Cubic field Trigonal field

doublet separation is large compared with kT because the orbital contribution is effectively quenched in the singlet if the doublet is of the order of 2000 cm.$^{-1}$ higher. This system is then analogous to V^{3+} complexes in an octahedral environment where splittings of this order are assumed to occur in the case of the vanadium alum.[13] A field of symmetry lower than cubic is probably present in both the triphenylphosphine- and the nitrosyl-hydroxy-nickel complex because of their unsymmetrical structures. However, the large value obtained for the Curie–Weiss constant may imply that there is antiferromagnetic interaction occurring in the nitrosyl hydroxy-complexes.

[10] Katzin, *Nature*, 1958, **182**, 1013.
[11] Weyl, "Quelques problèmes de chimie minérale," X Solvay Conseil de Chimie, Brussels, 1956, p. 420.
[12] Gill, Nyholm, and Pauling, *Nature*, 1958, **182**, 168.
[13] van der Handel and Siegert, *Physica*, 1937, **4**, 871.

The methoxy-complex,[4,5,7] previously formulated as $Ni(NO)(OH)(MeOH)_2$ is prepared by the action of dry nitric oxide on methanolic nickel tetracarbonyl.[4] Anderson [6,7] concluded that it was best formulated as $Ni(NO)(OH)(MeOH)_2$, although he pointed out that the analyses [6] better fitted the formula $Ni(NO)(OH)(OMe)_2$, which we now accept as correct. Since the infrared NO^+ stretching frequency (Table 2) and magnetic susceptibility (Table 3) are substantially the same as for $Ni(NO)(OH)_3$, it seems clear that the latter structure is probably the correct one.

Anderson also prepared in ethanolic solution a complex which he formulated as $Ni(NO)(OEt)(H_2O)$. We have re-examined this (Tables 2 and 3); it is clearly of the same

TABLE 3. *Magnetic susceptibility measurements on alkoxides at 22°.*

Complex	χ_g (c.g.s.u. × 10^{-6})	$\mu_{eff.}$ (B.M.)	Diamagnetic corrections (c.g.s.u. × 10^{-6})
$Ni(NO)(OH)(OMe)_2$	1·94	2·8	50
$Ni(NO)(OEt)_2OH$ + $Ni(NO)(OEt)(OH)_2$	1·96	2·8	80
$[Ni(NO_2)(OMe)(MeOH)]_2$	4·2	3·3	43
$Fe_2(NO)_2(OMe)(OH)(MeOH)_2$	2·88	2·97	40

structure as the methoxide, but the analyses do not fit the formulation $Ni(NO)(OH)_2(OEt)$. We suggest that it is in fact a mixture of $Ni(NO)(OH)(OEt)_2$ and $Ni(NO)(OH)_2(OEt)$. Since it is not possible to recrystallise these compounds, it is difficult to confirm this point; separation by chromatography might be possible, but the compounds are sensitive to air and are spontaneously transformed into the green nitro-form (see below), so that this would be technically difficult.

We have also prepared similar complexes with *n*-propyl, *n*-butyl, and *n*-pentyl alcohols (Table 2). They are all considered to have structures similar to $Ni(NO)(OMe)_2(OH)$, but analyses are variable owing to the increasing instability of the complexes as the alcoholic chain-length increases. They may all be regarded as mixtures of complexes of the form $Ni(NO)(OR)_n(OH)_{3-n}$.

The deep blue $Ni(NO)(OMe)_2(OH)$ changes [4,6,7] spontaneously in the course of a day to a green complex which, though it had the same analytical composition, had no reducing power. No gas is evolved or absorbed during the change. We have noted the same phenomenon in the blue ethanol, *n*-propanol, *n*-butanol, and *n*-pentanol complexes, although the change is slower the greater the chain length of the alcohol.

Anderson [7] suggested that, in view of the loss of reducing power of nickel, a hyponitrite complex is formed (cf. $[Co(NH_3)_5NO]_2Cl_4$). A recent study of such complexes [14] has shown that a characteristic infrared absorption band is observed in the 1000—1200 $cm.^{-1}$ region; no such bands arise in these green nickel complexes.

However, we have observed that the NO^+ band at 1820 $cm.^{-1}$ disappears in the green complexes, and is replaced by strong bands at 845 and 1270 $cm.^{-1}$ together with a weaker band at 1420 $cm.^{-1}$. Such absorption is characteristic of bridging nitro-groups.[15] Magnetic measurements (Table 3) show that the complex retains two unpaired electrons. The visible absorption spectrum shows a strong peak at 470 mμ.

It therefore seems likely that the green complexes are formed by a reaction of the type known to occur in nitroprussides,[16] and which is believed to occur in certain nitrosyl-platinum complexes:[17]

$$NO^+ + OH^- \longrightarrow NO_2^- + H^+$$

so, in this case the reaction is

$$Ni(NO)(OH)(OMe)_2 \longrightarrow Ni(NO_2)(OMe)(MeOH)$$

[14] Griffith, Lewis, and Wilkinson, *Physica*, 1937, **4**, 38.
[15] Nakamoto, Fujita, and Murata, *J. Amer. Chem. Soc.*, 1958, **80**, 4817.
[16] Cambi and Szego, *Atti R. Accad. Lincei*, 1927, **5**, 737; Hantzsch, *Z. phys. Chem.*, 1909, **65**, 57.
[17] Lewis, unpublished observations.

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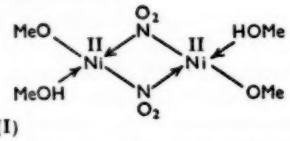
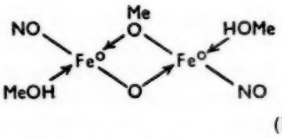
We can hence write the structural unit for the complex as (I), which will have analyses identical with those of the blue complex, as is found. The green colour of the complex both in the solid state and in methanolic solution indicates octahedral co-ordination of the metal atom; in the solid this could be achieved by further polymerisation through methoxy-bridges.

(2) *Dimethanol-μ-hydroxy-μ-methoxydinitrosyldi-iron*(0).—$Fe_2(NO)_2(OMe)(OH)(MeOH)_2$ was first prepared by Manchot and Gall [18] and formulated by them as $Fe(NO)(MeOH)_2$. It was later examined by Reihlen *et al.*[4a] who, after extensive analyses, assigned the formula $Fe_2(NO)_2(MeOH)_3OH$. As with the nickel compounds, the extreme instability of the complex renders precise measurements difficult. Infrared spectra (Table 2) show the presence of only one NO^+ stretching frequency and magnetic susceptibility measurements made at room temperatures on several samples (Table 3) indicate the presence of two unpaired electrons. From this evidence, the most reasonable formulation is (II), with tetrahedral (sp^3) zerovalent iron. Attempts were made to prepare analogues of this with higher alcohols, but only the ethanol complex could be isolated. It was less stable than the methoxide, but had a similar infrared spectrum. It was too unstable to permit reliable measurements.



(I)



(II)

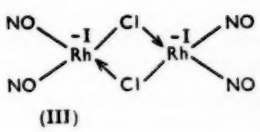
It is interesting to compare the paramagnetism of these complexes with the diamagnetism that occurs in Roussin's red series of compounds which have bridging sulphur atoms. In the latter, the iron atom has a formal valency of −1 and the odd electron on each iron atom is paired to give a diamagnetic complex. The Fe–Fe bond distance in the ethyl ester is 2·72 Å,[19] which is longer than can be expected for a Fe–Fe single bond, $Fe_2(CO)_9$ being taken as an example (Fe–Fe = 2·46 Å). If we assume that the spin-coupling operates through the bridging sulphur atoms, presumably owing to the participation of the 3*d* orbitals of sulphur, the paramagnetism of the oxygen-bridged system is understandable since with oxygen the suitable *d* orbitals are, of course, inaccessible.

(3) *Nitric Oxide–Halide Complexes of Palladium and Rhodium.—Palladium*(0) *dinitrosyl dichloride*, $Pd(NO)_2Cl_2$. This dichloride, and the disulphate, was prepared by Manchot and Waldmüller [20] by passing nitric oxide into methanolic palladous chloride or sulphate. It is unstable, evolving nitric oxide at high temperatures or in moist air. We have found it to be diamagnetic and to show two peaks in the NO^+ stretching region (Table 3). The most reasonable structure is hence $Pd(NO)_2Cl_2$, which involves Pd^0 with sp^3 tetrahedral bonding, and is thus related to the nitrosyl hydroxy-complexes of nickel. The instability of the complex is understandable on the grounds of the monomeric nature and low valency of the metal atom.

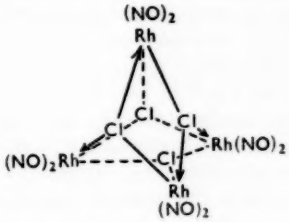
Rhodium(−1) *dinitrosyl chloride*, $Rh(NO)_2Cl$. This was first prepared by Manchot and König [21] by passing dry nitric oxide at 60° over $Rh(CO)_2Cl$ for 2 days. The resulting black substance he formulated as $RhO,3NO,RhCl_2$. We have examined the magnetic susceptibility and infrared spectra of this complex. The analyses which we obtain closely fit the stoicheiometry $Rh(NO)_2Cl$. It is diamagnetic, and the infrared spectrum in a mull shows two peaks in the NO^+ stretching region (Table 2). It is unreactive and is insoluble in water and most other solvents; attempts to sublime it result in decomposition. These facts suggest that the compound is polymeric and may have one of the structures (III) or (IV). Both would give two infrared-active NO^+ stretching frequencies and both would

[18] Manchot and Gall, *Annalen*, 1929, **470**, 271.
[19] Thomas, Robertson, and Cox, *Acta Cryst.*, 1958, **11**, 599.
[20] Manchot and Waldmüller, *Ber.*, 1926, **59**, 2363.
[21] Manchot and König, *ibid.*, 1927, **60**, 2130.

make the rhodium diamagnetic. The first structure is analogous to that of $[Co(NO)_2I)]_2$.[22] The second, involving five-co-ordination for the metal atom, is the analogue of $[Ni(NO)I]_4$;[23] such a halogen-bridged structure has been proved for the complexes $[Cu(AsL_3)I]_4$.[24]



(III)



(IV)

The insolubility and general inertness of the rhodium complex favour the latter structure, so we suggest it for the compound.

(4) *Nitric Oxide Cyano-complex of Cobalt.*—*Potassium cyanonitrosyldicarbonylcobaltate*(−I), $K[Co(CN)(NO)(CO)_2]$. This was prepared by Nast and Rohmer [25] from potassium cyanide and cobalt carbonyl nitrosyl. It is diamagnetic.[25] There are two possible structures: square planar (dsp^2) hybridisation of the cobalt, in which case the complex would be isoelectronic with $[Co^{I}(CN)_3CO]^{2-}$,[26] with NO donating as NO^-, as in $[Co(CN)_5NO]^{3-}$;[14] or tetrahedral (sp^3) hybridisation, with the complex isoelectronic with $Co^{I}(CO)_3NO$ and $Co^{-I}(CO)_4H$ (NO donating as NO^+). That the latter is the correct structure is shown by the presence of an intense NO^+ stretching frequency, together with one CN and two CO such frequencies (Table 2).

Experimental

The nitric oxide hydroxy- and alkoxy-nickel *complexes* were prepared as described by Anderson. His extensive analyses for the hydroxide and methoxide fit the revised formulation [Found: Ni, 44·1; N, 10·2. $Ni(NO)(OH)_3$ requires Ni, 42·0; N, 10·0%. Found: Ni, 35·2; N, 7·7; C, 14·5; H, 4·4. $Ni(NO)(OMe)_2OH$ requires Ni, 35·0; N, 8·4; C, 14·3; H, 4·2%]. For the ethoxide, a mixture of $Ni(NO)(OEt)(OH)_2$ and $Ni(NO)(OEt)_2(OH)$ in the ratio 5 : 1 is suggested by the analyses (Found:[6] Ni, 38·0; N, 9·6; O, 16·0; H, 4·0. Calc.: Ni, 35·0; N, 8·2; C, 15·8; H, 4·1%). The high values for nickel are almost certainly due to traces of $Ni(OH)_2$,[6] to which these complexes very readily decompose.

$Fe_2(NO)_2(MeOH)_2(OMe)(OH)$ was prepared by Reihlen and his collaborators' method,[40] and the new formulation fits the original analyses (Found: Fe, 39·8; C, 13·0; N, 10·0; H, 3·5. Calc.: Fe, 39·6; C, 12·8; N, 9·9; H, 3·6%).

$Pd(NO)_2Cl_2$ was prepared according to Manchot and Waldmüller [20] (Found: Pd, 44·9. Calc.: Pd, 44·3%). $Rh(NO)_2Cl$ was prepared according to Manchot and König [21] and re-analysed [Found: Rh, 50·9; Cl, 18·5; NO, 30·8. Calc. for $Rh(NO)_2Cl$: Rh, 50·6; Cl, 17·9; NO, 30·25%].

$K[Co(CN)(CO)_2(NO)]$ was prepared as by Nast and Rohmer.[25]

Physical Measurements.—Infrared spectra were measured on a Perkin-Elmer Model 21 recording spectrophotometer with sodium chloride and calcium fluoride optics. Absorption spectra were taken on a Perkin-Elmer recording spectrophotometer, model 4000. Magnetic susceptibilities were measured on solid samples on a Gouy balance.

One of us (W. P. G.) thanks the Department of Scientific and Industrial Research for a maintenance grant. We are also indebted to Johnson, Matthey and Co. Ltd. for the loan of palladium and rhodium chlorides.

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Imperial College, London, S.W.7. [*Received, December 23rd*, 1958.]

[22] Hieber, Beck, and Jahn, *Z. Naturforsch.*, 1958, **13**b, 194, 196.
[23] Hieber and Nast, F.I.A.T. Review of German Science 1939—1946, Inorganic Chemistry, Part II, 146.
[24] Mann, Purdie, and Wells, *J.*, 1936, 1503.
[25] Nast and Rohmer, *Z. anorg. Chem.*, 1956, **285**, 271.
[26] Hieber and Bartenstein, *ibid.*, 1954, **276**, 1.

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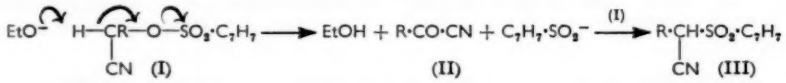
353. *Elimination of Sulphinate from Sulphonic Esters.*

By J. D. Loudon and I. Wellings.

Arenesulphonates of mandelonitriles are prepared by the action of potassium cyanide on the appropriate benzaldehyde and sulphonyl chloride. In contrast to the replacement of the sulphonate group, which characterises their reactions with most nucleophilic reagents, the esters eliminate the arenesulphinate ion when treated with sodium ethoxide in ethanol.

The sulphone (III; R = *o*-NO_2·C_6H_4) was an unexpected product of an attempted condensation between sodiomalonic ester and the toluene-*p*-sulphonate (I; R = *o*-NO_2·C_6H_4) of *o*-nitromandelonitrile. Investigation showed that this was the result of a two-stage process in which the toluene-*p*-sulphonate first furnished and then reacted with toluene-*p*-sulphinate anions. So far as we are aware the elimination of sulphinate from a sulphonic ester has not been observed previously although, among others, a close analogy is provided by the hydrolytic elimination of nitrite from nitric esters.[1]



R·CO·CHR·SO_2·C_7H_7 (IV) R·CO·CH_2·S·SO_2·C_7H_7 (V) R·CO·CH_2·NR·SO_2Ph (VI)

α-Cyanobenzyl sulphonates have not been studied extensively. Those derived from mandelonitrile are prepared by the interaction of benzaldehyde, potassium cyanide, and a sulphonyl chloride.[2,3] Although the method is said [4] to fail with other arylaldehydes as reagents, a satisfactory extension may be achieved in many cases (see Experimental section). As non-lachrymatory substitutes for α-cyanobenzyl halides the sulphonates react with thiourea,[3] substituted thioureas, dithiocarbamates, or thioamides,[5] forming appropriate derivatives of thiazole. With sulphonyl chlorides in presence of thiourea they yield alkyl- or aryl-sulphonylacetonitriles,[6] and under Friedel–Crafts conditions condense with aromatic compounds affording diarylacetonitriles.[4] The nucleophilic displacement of the sulphonate group, implicit in these reactions, is supplemented by our own observations which, while not systematic, provide examples of sulphonate replacement under attack by bromide, mercaptide, *p*-nitrophenoxide and toluene-*p*-sulphinate ions. It may also be noted that hydrogenation of 2-chloro-α-cyanobenzyl toluene-*p*-sulphonate with palladised charcoal as catalyst affords 2-chlorophenethylamine, recalling the similar hydrogenation of *O*-acylmandelonitriles.[7]

In sharp contrast to the foregoing reactions α-cyanobenzyl toluene-*p*-sulphonates react with sodium ethoxide in cold anhydrous ethanol, affording sodium toluene-*p*-sulphinate in high yield (*ca.* 90%). In each case the other immediate product is undoubtedly the benzoyl cyanide (II), but this undergoes further reaction so that the isolated product is the ethyl ester (or sodium salt) of the corresponding benzoic acid. It is interesting that under these conditions elimination of sulphinate is virtually complete and outstrips formation of the sulphone (III). The sulphone was formed when 2-chloro-α-cyanobenzyl toluene-*p*-sulphonate was heated with triethylamine, whereas the same ester with pyridine gave a pyridinium salt from which a betaine type of product, $C_5H_5\overset{+}{N}-\overset{-}{C}(CN)\cdot C_6H_4Cl$, was obtained by treatment with alkali.

[1] Baker and Easty, *J.*, 1952, 1193.
[2] Francis and Davis, *J.*, 1909, **95**, 1403.
[3] Dodson and Turner, *J. Amer. Chem. Soc.*, 1951, **73**, 4517.
[4] Sisido, Nozaki, Nozaki, and Okano, *J. Org. Chem.*, 1954, **19**, 1699.
[5] Taylor, Wolinsky, and Lee, *J. Amer. Chem. Soc.*, 1954, **76**, 1866, 1870; Taylor, Anderson, and Berchtold, *ibid.*, 1955, **77**, 5444.
[6] Dodson, U.S.P. 2,748,164; cf. *Chem. Abs.*, 1957, **51**, 2860.
[7] Kindler, *Arch. Pharm.*, 1931, **269**, 70.

It seems reasonable to expect that sulphinate elimination should also be observable from sulphonic esters of type (IV), from thiolsulphonic esters of type (V), and from sulphonamides of type (VI). The benzenesulphonate of benzoin [8] and the toluene-*p*-sulphonate of 2-oxo-3-phenylpropan-1-ol were accordingly prepared and examined, but elimination of sulphinate was not detected. Attempts to prepare phenacyl toluene-*p*-thiolsulphonates (V; R = Ar) from phenacyl bromides led chiefly to phenacyl *p*-tolyl sulphones presumably *via* sodium toluene-*p*-sulphinate formed by decomposition of the sodium toluene-*p*-thiolsulphonate used as a reagent. On the other hand, Takata [9] has shown that compounds allied to type (VI) yield sulphinates when heated with potassium ethoxide in non-hydroxylic solvents. This we have confirmed for the particular case (VI; R = R = Ph) and have shown that the oil (phenylglyoxal or its anil) simultaneously formed affords 2-phenylquinoxaline in reaction with *o*-phenylenediamine.

Experimental

α-Cyanobenzyl Arenesulphonates (I).—In a typical preparation potassium cyanide (0·66 g.) was added with stirring to a solution of *o*-chlorobenzaldehyde (1·4 g.) and toluene-*p*-sulphonyl chloride (1·9 g.) in dioxan (2 c.c.) and water (4 c.c.), the temperature being kept below 5° and stirring continued for 1 hr. The solid was collected, dissolved in a mixture of acetone, ethanol, and water (5 c.c.; 2 : 2 : 1), filtered if necessary, and treated with ice (3 g.), affording the crude product.

α-Cyano(substituted)benzyl toluene-p-*sulphonates* (I)

Subst.	M. p.	Yield (%)	Formula	Found (%) C	H	N	Required (%) C	H	N
H	60° [a]	72							
2-Br	104	75	$C_{15}H_{12}O_3NBrS$	49·4	3·2	3·9	49·2	3·3	3·8
2-Cl	86	78	$C_{15}H_{12}O_3NClS$	55·9	3·6	4·6	56·0	3·7	4·4
3-MeO	52	55	$C_{16}H_{15}O_4NS$	60·5	4·7	4·4	60·6	4·8	4·4
2-NO_2	111	72	$C_{15}H_{12}O_6N_2S$	54·1	3·9	8·3	54·2	3·6	8·4
2 : 4-Cl_2	78	72	$C_{15}H_{11}O_3NCl_2S$	50·6	3·4	4·0	50·5	3·2	3·9
2-Cl-5-NO_2	118 *	70	$C_{15}H_{11}O_5N_2ClS$	49·3	3·4	7·7	49·2	3·1	7·6

* From benzene–light petroleum (b. p. 60—80°): the others from ethanol.

From 2 : 5-dichlorobenzenesulphonyl chloride there were prepared in the same way *α-cyanobenzyl*, m. p. 102° (from ether) (Found: C, 49·0; H, 2·6; N, 4·5. $C_{14}H_9O_3NCl_2S$ requires C, 49·1; H, 2·6; N, 4·1%), and *4-chloro-α-cyanobenzyl* 2 : 5-*dichlorobenzenesulphonate*, m. p. 86° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 44·8; H, 2·2; N, 4·3. $C_{14}H_8O_3NCl_3S$ requires C, 44·8; H, 2·1; N, 3·7%).

Elimination of Sulphinate.—(i) A solution of sodium ethoxide (from 0·12 g. of sodium in 2 c.c. of ethanol) was added to a solution of α-cyano-2-nitrobenzyl toluene-*p*-sulphonate (1·66 g.) in ethanol (10 c.c.). After 15 min. the solvent was removed *in vacuo* and the residue was extracted with benzene, leaving sodium toluene-*p*-sulphinate (0·77 g.) which was identified as the sulphinic acid (m. p. and mixed m. p. 84°) and as the derived 2 : 4-dinitrophenyl sulphone (m. p. and mixed m. p. 187°). Chromatography of the benzene solution on alumina afforded ethyl *o*-nitrobenzoate (0·68 g.), m. p. 30° (Found: N, 7·3. Calc. for $C_9H_9O_4N$: N, 7·2%), which was hydrolysed to *o*-nitrobenzoic acid (m. p. and mixed m. p. 147°).

(ii) High yields of the appropriate sulphinic acid were likewise obtained from the other sulphonates described above. 2 : 5-Dichlorobenzenesulphinic acid had m. p. and mixed m. p. 122°.

(iii) When the sodium ethoxide of (i) was replaced by diethyl sodiomalonate the solid precipitated in the reaction contained (water-soluble) sodium toluene-*p*-sulphinate and α-cyano-2-nitrobenzyl *p*-tolyl sulphone, m. p. and mixed m. p. 167° (cf. below). An oil, recovered from the reaction mother-liquor, was hydrolysed by 5N-sodium hydroxide, affording *o*-nitrobenzoic acid.

[8] Zoldi, *Ber.*, 1927, **60**, 656.
[9] Takata, *J. Pharm. Soc., Japan*, 1951, **71**, 1474.

(iv) 2-Chloro-α-cyanobenzyl toluene-*p*-sulphonate (1·5 g.) was heated for 30 min. with triethylamine (5 c.c.) at 100°. The oil obtained by concentration *in vacuo* was rubbed with benzene–light petroleum (b. p. 60—80°; 1 : 1) affording 2-chloro-α-cyanobenzyl *p*-tolyl sulphone, m. p. and mixed m. p. 112° (cf. below), and an oily extract which, after hydrolysis, yielded *o*-chlorobenzoic acid, m. p. and mixed m. p. 142°.

(v) *From* N-*phenacylbenzenesulphonanilide.* Ethanolic solutions of the anilide [9] (0·73 g. in 10 c.c.) and sodium ethoxide (from 0·046 g. of sodium in 3 c.c.) were mixed and after 30 min. the precipitated sodium toluene-*p*-sulphinate was collected and identified as in (i). An ethereal extract of the evaporated filtrate afforded an oil which, with *o*-phenylenediamine in warm ethanol, yielded 2-phenylquinoxaline,[10] m. p. 78° (Found: C, 81·6; H, 4·7; N, 13·2. Calc. for $C_{14}H_{10}N_2$: C, 81·5; H, 4·9; N, 13·6%).

Replacement of Sulphonate.—α-Cyanobenzyl bromide, b. p. 137—139°/15 mm., m. p. 29°, was recovered in ether (yield 70%) after a solution of α-cyanobenzyl toluene-*p*-sulphonate (2·87 g.) in methanol (20 c.c.) had been heated with sodium bromide (1·53 g.) under reflux for 1 hr., and the resultant mixture concentrated.

2-*Chloro-α-cyanobenzyl* p-*tolyl sulphide*, m. p. 62° (from methanol), was obtained (yield 85%) when a solution of 2-chloro-α-cyanobenzyl toluene-*p*-sulphonate (0·32 g.), thio-*p*-cresol (0·13 g.), and sodium hydroxide (0·04 g.) in ethanol–water (8 c.c.; 4 : 1) was heated under reflux for 30 min. (Found: C, 65·7; H, 4·1; N, 5·3. $C_{15}H_{12}NClS$ requires C, 65·8; H, 4·3; N, 5·1%).

2-*Chloro-α-cyanobenzyl* p-*tolyl sulphone*, m. p. 112° (from ethanol), crystallised from a refluxing solution of 2-chloro-α-cyanobenzyl toluene-*p*-sulphonate (0·32 g.) and sodium toluene-*p*-sulphinate (0·27 g.) in ethanol (5 c.c.) (Found: C, 59·0; H, 4·1; N, 4·8. $C_{15}H_{12}O_2NClS$ requires C, 59·0; H, 4·0; N, 4·6%). α-*Cyano*-2-*nitrobenzyl* p-*tolyl sulphone*, m. p. 167° (from ethanol) (Found: C, 56·8; H, 3·8; N, 8·8. $C_{15}H_{12}O_4N_2S$ requires C, 57·0; H, 3·8; N, 8·9%), and α-*cyanobenzyl* p-*tolyl sulphone*, m. p. 152° (Found: C, 66·3; , 4·8; N, 5·4. $C_{15}H_{13}O_2NS$ requires C, 66·4; H, 4·8; N, 5·2%), were similarly prepared from the appropriate toluene-*p*-sulphonates.

α-*Cyano*-2-*nitrobenzyl* p-*nitrophenyl ether*, m. p. 157° (from ethanol), was recovered in ether after concentration of the mixture formed by heating sodium *p*-nitrophenoxide and α-cyano-2-nitrobenzyl toluene-*p*-sulphonate in ethanol for 48 hr. (Found: C, 56·2; H, 2·8; N, 13·9. $C_{14}H_9O_5N_3$ requires C, 56·2; H, 3·0; N, 14·0%).

1-(2-*Chloro-α-cyanobenzyl*)*pyridinium toluene*-p-*sulphonate* slowly crystallised at 0° from a solution of 2-chloro-α-cyanobenzyl toluene-*p*-sulphonate (1·6 g.) in anhydrous pyridine (2 c.c.). It formed colourless crystals, m. p. 101° [from benzene–light petroleum (b. p. 60—80°) containing a trace of ethanol] (Found: C, 60·5; H, 4·2; N, 6·8. $C_{20}H_{17}O_3N_2ClS$ requires C, 60·0; H, 4·2; N, 7·0%), and when treated with 5N-sodium hydroxide afforded a *betaine* as dark red crystals, m. p. 138° (from ethanol) (Found: C, 68·5; H, 4·2; N, 12·1. $C_5H_5\overset{+}{N}-\overset{-}{C}(CN)\cdot C_6H_4Cl$ requires C, 68·3; H, 3·9; N, 12·3%).

2-*Chlorophenethylamine.*—2-Chloro-α-cyanobenzyl toluene-*p*-sulphonate (0·32 g.) was hydrogenated in acetic acid (3 c.c.) containing concentrated sulphuric acid (0·05 c.c.) and in presence of 10% palladium–charcoal (0·15 g.). Absorption of hydrogen (3 mol.) was complete after 3 hr. The filtered solution was basified and the amine, recovered in ether, was precipitated as the picrate,[11] m. p. 186° (from benzene; yield 60%) (Found: C, 44·2; H, 3·3; N, 14·5. Calc. for $C_{14}H_{13}O_7N_4Cl$: C, 43·7; H, 3·4; N, 14·6%).

[With G. Tennant.] 2-*Oxo*-3-*phenylpropyl Toluene*-p-*sulphonate.*—To a stirred solution of diazomethane (~10 g.) in anhydrous ether (500 c.c.) was added phenacetyl chloride (15·5 g.) in ether (50 c.c.) and, after several hours, powdered toluene-*p*-sulphonic acid (17 g.). After 12 hr. at 20° the solvent was removed and the gummy solid afforded the *ester*, m. p. 63° (from ethanol) (Found: C, 63·0; H, 5·4. $C_{16}H_{16}O_4S$ requires C, 63·15; H, 5·3%).

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[10] Hinsberg, *Annalen*, 1896, **292**, 246.
[11] Goodson, *et al.*, *Brit. J. Pharmacol.*, 1948, **3**, 49.

354. *Reaction Mechanisms in Organometallic Compounds. Comparative Solvolyses of Organotin and Organosilicon Chlorides.*

By R. H. Prince.

The solvolyses of organotin chlorides R_3SnCl (R = Et, Pr^i, Bu^t, Ph) in ethanol, propan-2-ol, and water–dioxan have been studied. The behaviours of tin and silicon have been compared in solvolysis and hydrolysis of the tri*iso*propyl halides in propan-2-ol.

Alcoholysis and hydrolysis of organotin halides are rapid to positions of equilibrium which depend upon the medium and the nature of the alkyl group. When the latter is *iso*propyl and in propan-2-ol rates are measurable; when it is *tert.*-butyl solvolysis rates are measurable in ethanol and in propan-2-ol but solvolytic equilibrium lies further in favour of the undissociated halide. The solvolysis of tri*iso*propylsilyl chloride in propan-2-ol has an abnormally low steric factor and is catalysed by pyridine; hydrolysis in propan-2-ol is of second order and is not catalysed by pyridine.

Potentiometric, conductivity, and rate data are consistent with a synchronous displacement at tin and silicon in which steric effects are important in determining reactivity.

Although the mechanism of substitution at a saturated carbon atom is now well understood [1] kinetic–mechanistic studies of organosilicon halides are few [2-4] and none exists of organotin halides. Kinetic data on organosilicon halides have been interpreted in terms of (*a*) a quinquecovalent intermediate [2,4] and (*b*) a synchronous mechanism in which bond-making between silicon and the attacking nucleophile is dominant.[3] The balance of evidence on sterically-hindered monochlorosilanes favours the latter. There is no kinetic evidence for an S_N1 substitution at silicon; indeed the only siliconium ion appears to be the optically active sexaco-ordinated ion $(acac)_3Si^+$ (acac = acetylacetone).[5] Silicon halides are much more rapidly solvolysed than are carbon halides of analogous structure, and in chlorides R_3SiCl (R = alkyl) rates of substitution show marked dependence on the steric effectiveness of the alkyl group: only when R is branched (or is a bulky aromatic group) are rates measurable. Previous comparison of triorgano-silicon and -tin compounds [6] indicated than when R is simple rapid reactions are observed, but, whereas ethanolysis and hydrolysis of organosilicon compounds are essentially complete, with organotin compounds an equilibrium is reached.[6-8]

This paper describes the solvolysis of the halides R_3SnCl (R = Et, Pr^i, Bu^t, and Ph) in ethanol, propan-2-ol, and water–dioxan; comparison is made of the *iso*propyl compound with that of silicon.

Experimental

Preparation of Materials.—Triethyltin chloride. Commercial triethyltin hydroxide was treated with hydrochloric acid followed by potassium hydroxide, and filtered to remove diethyltin oxide; the hydroxide was reconverted into the chloride and purified by molecular distillation. The product contained traces of tetraethyltin which were allowed for subsequently.

Triisopropyltin chloride and diisopropyltin dichloride. Stannic chloride–ether complex (0·063 mole) was alkylated with the stoicheiometric amount of *iso*propyl-lithium for formation of the trialkyl compound (0·189 mole; prepared in ether at −40°); a mixture of tetra*iso*propyltin and the mono- and di-chlorides in approximately equal amounts was obtained. The

[1] Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, ch. 7.
[2] Swain, Esteve, and Jones, *J. Amer. Chem. Soc.*, 1949, **71**, 943.
[3] Hughes, *Quart. Rev.*, 1951, **5**, 245; Allen, Charlton, Eaborn, and Modena, *J.*, 1957, 3668; Allen and Modena, *J.*, 1957, 3671.
[4] Shaffer and Flanigen, *J. Phys. Chem.*, 1957, **61**, 1591.
[5] Dhar, Doron, and Kirschner, *J. Amer. Chem. Soc.*, 1958, **80**, 753.
[6] Dennison, Thesis, London University, 1954.
[7] Rochow and Seyferth, *J. Amer. Chem. Soc.*, 1953, **75**, 2877.
[8] Kraus and Callis, *ibid.*, 1923, **45**, 2624; Kraus and Greer, *ibid.*, p. 2946.

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dichloride was isolated by molecular distillation and resublimed *in vacuo* (Found: Cl, 25·0. Calc. for $C_6H_{14}Cl_2Sn$: Cl, 25·7%).

The monochloride was prepared [9] from the tetra-alkyltin, which was obtained by addition of stannic chloride (0·063 mole) to excess of *iso*propylmagnesium bromide (2 mol.) in ether. The ether was distilled off and the residue kept at 100° for 1 hr.; fractionation gave tetra*iso*propyltin (61·2 g.; 61%), b. p. 100·6—101·2°/8 mm. This was treated with stannic bromide (⅓ mol.) at 125—165°. The liquid phase consisted mainly of the monobromide (~90% w/w); unchanged tetra-alkyl and dibromide were removed by the following treatment which depends upon the insolubility of the alkyltin fluorides and the polymeric dialkyltin oxides. The mixture in ether was treated with a 20% w/v solution of potassium fluoride in 60% aqueous ethanol: the precipitated fluorides (Pr^i_3SnF, $Pr^i_2SnF_2$) were filtered off, extracted with ether to remove tetra*iso*propyltin, and then treated with concentrated hydrochloric acid and extracted with ether. The extract was treated with 10% w/v sodium hydroxide; the precipitated oxide $(Pr^i_2SnO)_n$ was filtered off. The filtrate ($Pr^i_3Sn{\cdot}OH$) in ether was converted into the chloride

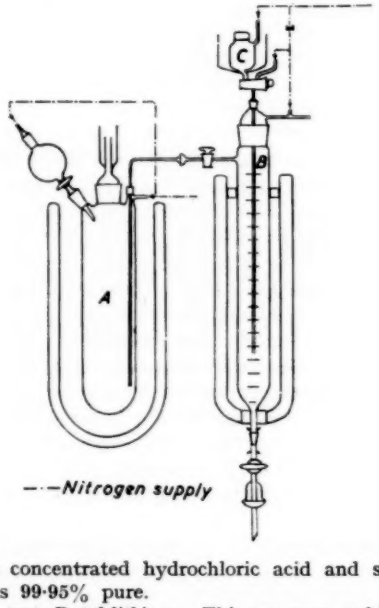

FIG. 1. *Apparatus for the preparation of* tert.-*butyllithium in ether at low temperature.*

by concentrated hydrochloric acid and subjected to molecular distillation. The product was 99·95% pure.

tert.-*Butyl-lithium.* This was prepared by treatment of excess of lithium sand or wire with *tert.*-butyl chloride in ether at −55° to −60° for 4—4½ hr.

tert.-Butyl-lithium attacks ether; in the controlled alkylation of stannic chloride with ethereal *tert.*-butyl-lithium the concentration of derivative was determined by double titration in which the alkali formed by hydrolysis was titrated before and after coupling of the derivative with benzyl chloride.[10]

tert.-Butyl-lithium was prepared in a 400-ml. vessel kept at −55° to −65° (Fig. 1; *A*). When all the alkyl chloride had been added the temperature was lowered to −80°, and lithium chloride allowed to settle. The clear solution was then transferred by pressure of nitrogen to a 3·5 × 40 cm. tube (*B*) graduated in 10-ml. divisions. Samples of solution were transferred to a small vessel (*C*) by nitrogen pressure and removed for analysis by a 2-ml. hypodermic syringe *via* a vaccine-cap closure. The solution was then added to the calculated quantity of stannic chloride–ether complex.

Di-tert.-*butyltin dichloride and tri*-tert.-*butyltin chloride.*—The alkyl-lithium was added to a suspension of the stannic chloride–ether complex at 0°: addition in reverse order caused

[9] Kocheskov, *Ber.*, 1933, **66**, 1661; *J. Gen. Chem. Russia*, 1934, **4**, 1359; 1935, **5**, 211.
[10] (*a*) Gilman and Haubein, *J. Amer. Chem. Soc.*, 1944, **66**, 1515; (*b*) Gilman and Clark, *J. Amer. Chem. Soc.*, 1947, **69**, 1499.

formation of coloured reduction products. Variation of the mole ratio $Bu^tLi : SnCl_4$ gave the following results. **3 : 1-*ratio*:** Alkylation to the monochloride was incomplete and a product containing 55% of the monochloride was isolated. Molecular distillation followed by centrifugation at −10° enabled half of the dichloride present to be isolated. Attempts to purify the residue by the fluoride–hydroxide method (above) were unsuccessful owing to the partial solubility of the dihydroxide, $Bu^t_2Sn(OH)_2$, in ether. **6 : 1 *ratio*:** A viscous liquid was isolated which gave a product containing 93% of monochloride on molecular distillation. **3·3 : 1 *ratio*:** A product containing 90% of monochloride was isolated. **3·0 : 1·05 *ratio*:** Treatment of the product in ether with potassium hydroxide gave a voluminous white precipitate; with concentrated hydrochloric acid this gave a 44% overall yield of the dichloride, which was purified by sublimation at 0·01 mm. (Found: Cl, 23·2. Calc. for $C_8H_{18}SnCl_2$: Cl, 23·35%).

The monochloride could not be obtained pure and the best sample (93% of monochloride) contained the dichloride as impurity. In solvolyses the effect of the dichloride was examined by separate solvolysis.

Triphenyltin chloride. Eastman Kodak material was recrystallised thrice from ethanol and sublimed *in vacuo* (m. p. 105°, lit., 104—108°). The material was 99% pure, the impurity being tetraphenyltin. Allowance was made for this in electrochemical experiments.

Triisopropylsilyl chloride. This was prepared as previously described [10b] (b. p. 75·2—75·5°/7·6 mm., Found: Cl, 18·3. Calc. for $C_9H_{21}SiCl$: Cl, 18·4%).

Ethanol and propanol. Ethanol was dried over calcium oxide and distilled twice from sodium and ethyl phthalate in a baked-out fractionation apparatus: the water content of the product was 0·002—0·004% w/v.

Analytical reagent, peroxide-free propan-2-ol was dried by three methods: (i) distillation from lithium; (ii) a column method with calcium sulphate as the stationary phase; (iii) distillation from magnesium and iodine. Method (i) was satisfactory for the preparation of alcohol with water content about 0·02% w/v. Method (ii) was used with (iii) to obtain the driest samples: after the water concentration had been reduced to 0·02—0·03% w/v by method (ii) the alcohol was refluxed with magnesium powder and iodine for 8 hr. and then fractionated with intermittent take-off. Samples prepared in this way had water contents in the range 0·001—0·002% w/v.

Dioxan. This was purified as described by Vogel.[11]

Determination of Water Concentration.—A method based on Fischer's reagent was used.[12] A " dead-stop " electrometric method located the end-point of the titration: when the rates of titration were kept constant, results having a coefficient of variation of ±2% were obtained for water-content levels from 0·002 to 0·01% w/v.

Conductivity Measurements.—Four cells of conventional design were calibrated: [13] the constants were $0·0790_3$, $0·0208_9$, $0·0395_0$, $0·0438_0$. In two of these provision was made for passing a stream of dry nitrogen through the cell contents to expedite mixing and for adding halide samples to solvent contained in the cell without ingress of atmospheric moisture.

A high precision A.C. bridge with Wagner earth [14] was used for measurements of cell constant and equilibrium. For conductometric runs the Philips GM 4249 direct-reading A.C. bridge was more suitable: it was calibrated with standard resistances, and the accuracy and repeatability were then better than ±1% in the range 10^2—10^7 ohm.

Results of Solvolysis Experiments.—Solvolyses of organotin halides were followed conductometrically and those of tri*iso*propylsilyl chloride conductometrically and titrimetrically.

Organotin halides. Under the following conditions equilibrium values of conductivity were reached too rapidly for rate measurements to be made at 0°: triethyltin chloride in ethanol [6] and in propan-2-ol; tri*iso*propyltin chloride in ethanol; triphenyltin chloride in ethanol–acetone. Even at −80° the rates were not observable by conventional kinetic means. Measurements of conductivity as a function of water concentration in the range 1—25 × 10^{-3}M and extrapolation to zero water concentration showed that the halide conducted in the alcohol independently of residual water in the solvent.[15]

Measurable rate effects were observed with the tri*iso*propyltin compound in propan-2-ol.

[11] Vogel, " Practical Organic Chemistry," Longmans, 1951, p. 175.
[12] Prince, *Analyst*, 1953, **78**, 607.
[13] Jones and Bradshaw, *J. Amer. Chem. Soc.*, 1933, **55**, 1780.
[14] Luder, *ibid.*, 1940, **62**, 89; Solomons, Thesis, London University, 1956.
[15] Rochow, Hurd, and Lewis, " The Chemistry of Organometallic Compounds," Wiley, 1957, p. 185; Rochow and Thomas, *J. Inorg. and Nuclear Chem.*, 1957, **4**, 205.

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The effect (Fig. 2) depends on water concentration and temperature. The initial decrease of cell resistance, although too rapid to give accurate kinetic data, is slower than that observed with triethyltin chloride where a step-wise change of conductivity occurs on addition to the solvent with rapid mixing. The only inorganic compound possibly present in the tri*iso*propyltin chloride is a trace of di*iso*propyltin dichloride. The effect of the dichloride was examined by solvolysis in propan-2-ol: a step-wise change of conductivity was observed when the sample was added to the solvent, followed by a slight drift during several hours which could not account for the effects found with the monochloride.

The specific conductivity of tri*iso*propyltin chloride at concentrations $\sim 10^{-3}$M in ethanol at 0° is of the order of $0{\cdot}2$—$0{\cdot}3 \times 10^{-6}$ ohm^{-1} cm.$^{-1}$: this is 10—15 times larger than the specific conductivity of propan-2-ol solutions under the same conditions. In the same alcohol the specific conductivity of solutions of the triethyl compound is 2—3 times larger than that of the tri*iso*propyl compound.

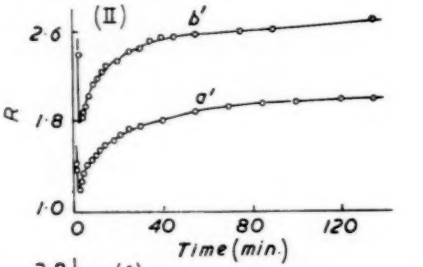


FIG. 2. *Resistance–time curves for solvolysis of tri*iso*propyltin chloride in propan-2-ol–water.*

R is cell resistance (ohm $\times 10^{-6}$). (I) Runs at 0°: (*a*) [Halide] 0·0125M, [H_2O] 0·040M; (*b*) [Halide] 0·0085M, [H_2O] 0·0102M; (*c*) [Halide] 0·0105M, [H_2O] < 0·0004M; (*d*) [Halide] 0·0091M, [H_2O] < 0·0004M. (II) Runs at 25°: [H_2O] in each case <0·0004M; (*a'*) [Halide] 0·0108M; (*b'*) [Halide] 0·0045M.

The equivalent conductivity of ethanol solutions of tri-*tert.*-butyltin chloride at equilibrium was lower than that of tri*iso*propyltin chloride solutions at the same concentration, but the equilibrium value was not attained instantaneously. The slow approach of the conductivity to equilibrium was attributed to the slow solvolysis of the halide by the alcohol since addition of traces of water caused immediate readjustment of the conductivity.

Rate effects in propan-2-ol were similar to those in ethanol except that water reacted at a measurable rate with the halide and the conductivity–time curve was of two parts: the first, shown by the effect of water addition to be due to attack by water, had a first-order constant 40 times as large as that of the second part: the latter was therefore attributed to the solvolysis of the halide. The first-order constants for solvolysis in ethanol and propan-2-ol obtained from the initial phase of the solvolysis are as follows [units are $10^4 k_1$ (in sec.$^{-1}$); R is the percentage of dichloride in the sample of the monochloride used].

Temp.	0°		25°	
R	7	45	7	45
Ethanol	3·4	10	33	46
Propan-2-ol	0·11	—	0·80	—

Solvolysis of di-*tert.*-butyltin dichloride alone gave a step-wise change of conductivity on addition to the solvent: the rate effects observed with the monochloride samples are therefore attributable to the monochloride. The rate is greater in the sample containing the greater dichloride content.

Triisopropylsilyl chloride. Solvolysis was examined in propan-2-ol and in propan-2-ol–water. Conductometric data were treated as follows. The rate equation for formation of ions by a first-order process is:

$$k_1 t/2{\cdot}303 = \log [(R_0 - R_\infty)/R_0] + \log [R_t/(R_t - R_\infty)]$$

where R_0 = cell resistance at zero time, R_t = cell resistance at time t, and R_∞ = the cell resistance at infinite time. It is assumed that the conductivity of the cell at any time is proportional to the concentration of ions formed at that time. The range of concentration of halide over which this assumption is valid is examined below

It is useful to test whether departure from this equation arises because ions are formed by a second-order process or by a first- + second-order one (*e.g.*, simultaneous alcoholysis by solvent and hydrolysis by small amounts of water present in the solvent). This can be done as follows: if α represents (cell resistance)$^{-1}$ and the subscripts are the same as before, then

$$a/(a - x) = (\alpha_\infty - \alpha_0)/(\alpha_\infty - \alpha_t) \text{ and } (b - x)/b = 1 - [a(\alpha_t - \alpha_0)/b(\alpha_\infty - \alpha_0)],$$

where a, b, and x have their usual significance. The equation for simultaneous first- and second-order reactions is:

$$dx/dt = k_1(a - x) + k_2(a - x)(b - x)$$

therefore

$$d \ln [a/(a - x)]/dt = k_1 + k_2(b - x)$$

and

$$d \ln [(\alpha_\infty - \alpha_0)/(\alpha_\infty - \alpha_t)]/dt = k_1 + k_2 b\{1 - [a(\alpha_t - \alpha_0)/b(\alpha_\infty - \alpha_0)]\}$$

Hence a plot of $d(\log [\alpha_\infty - \alpha_t])/dt$ against $[(\alpha_t - \alpha_0)/(\alpha_\infty - \alpha_0)]$ gives a straight line of slope $k_2 a/2{\cdot}303$ and intercept $-(k_1 + k_2 b)/2{\cdot}303$; given a and b the values of k_1 and k_2 can be found.

Analysis of conductivity–time curves in this way showed that at halide concentrations $\geqslant 2 \times 10^{-3}$M the data did not fit first-, first- + second-, or second-order kinetics: this was probably because proportionality between conductivity and ion concentration breaks down above this concentration. Below this concentration rates agreeing well with those obtained titrimetrically were observed: the assumption of proportionality is then valid.

At similar concentrations in the same solvent the specific conductivity of solutions of tri*iso*propylsilyl chloride was some 100 times larger than that of the corresponding tin compound.

Titrimetric data were analysed in the usual way: first- and second-order constants were derived from appropriate log plots. Runs were followed by removing aliquot parts at known time intervals after the addition of the halide to the alcohol, quenching the sample in dry acetone at −80°, and titrating the hydrochloric acid formed with ethanolic sodium ethoxide to a lacmoid end point. The end point was stable in presence of free halide for 15 minutes after titration.

An example of hydrolysis of tri*iso*propylsilyl chloride in propan-2-ol is as follows; $[k_1]_0$ is the value of the first-order constant at zero time:

$[H_2O]$ (M × 10^3)	18·4	22·25	32·45	37·9	45·4
$[Pr^i_3SiCl]$ (M × 10^3)	16·25	32·25	13·3	10·6	9·65
$10^3 k_2$ (l. mole^{-1} sec.$^{-1}$)	2·57	2·59	2·59	2·57	2·54
$10^4[k_1]_0$ (sec.$^{-1}$)	4·15	5·76	7·78	10·4	12·3

A plot of $[k_1]_0$ against $[H_2O]$ is a straight line giving $k_2 = 2{\cdot}5 \times 10^{-2}$ (l. mole^{-1} sec.$^{-1}$) The value of k_2 obtained from the second-order plots decreased after 60—70% of reaction; addition of pyridine resulted in a plot linear to 75—90% of reaction, k_2 remaining constant.

Alcoholysis by propan-2-ol at 44·6°, 59·1°, and 73·1° gave the following results:

Temp. (°)	44·6	44·6	59·1	73·1	73·1	73·1
[Py]			absent			
$[Pr^i_3SiCl]$ (M × 10^2)	3·21	7·31	7·11	4·43	4·79	5·13
$10^5 k_1$ (sec.$^{-1}$)	1·09	1·11	2·12	3·04	$3·04_5$	$3·04_5$
[Py]	0·17	0·17	—	3·97	8·60	—
$[Pr^i_3SiCl]$ (M × 10^3)	5·8	5·7	—	3·25	2·40	—
$10^5 k_1$ (sec.$^{-1}$)	1·89	2·02	—	5·82	5·64	—

XUM

Addition of pyridine increased the rate by a factor of two. The Arrhenius parameters for the solvolysis in absence of pyridine are E_A 9 kcal./mole and log PZ 1·3. It is evident that the same reaction has an unusually low steric factor.

tert.-*Butyl chloride in propan-2-ol at low concentrations of water.* For comparison with the data on organo-silicon and -tin halides the solvolysis of *tert.*-butyl chloride, which is typically an S_N1 process, was studied at 44·6°, 59·1°, and 73·1° in propan-2-ol containing ~0·02M of water, a sealed tube titrimetric technique being used. The concentration of hydrochloric acid formed during solvolysis goes through a maximum and then decreases with time: the maximum concentration is approximately equivalent to the water concentration. The initial rate as a function of temperature gave log PZ 10, E_A 24 kcal./mole.

Hydrolysis of organotin chlorides in dioxan–water. Tri*iso*propyltin chloride in dioxan–water showed the following behaviour when the water concentration was varied over a wide range; [Halide] $2{\cdot}00 \times 10^{-3}$M; κ = specific conductivity (ohm^{-1} cm.$^{-1}$ $\times$ 10^{10}); Λ_v = equivalent conductivity (ohm^{-1} cm.^{2} $\times$ 10^3).

[H_2O] (M) ...	2·13	2·29	2·56	2·97	3·16	3·46	3·78	4·64	5·15	5·53	6·82
κ	1·0	2·03	3·85	8·07	14·6	27·1	51·2	174	316	479	1553
Λ_v	0·052	0·104	0·217	0·425	0·773	1·44	2·74	9·46	17·3	26·4	88·0

At water concentrations less than 2M there was no significant conduction.

At every point the equilibrium conductivity value was reached within the time necessary for complete mixing of the components of the solution.

The effect of variation of R in R_3SnCl was studied in dioxan–water solutions of fixed composition (26% w/w of water): if water is present in large excess over the chloride, the dissociation $R_2SnCl + H_2O \rightleftharpoons R_2SnOH_2^+ + Cl^-$ should obey the dilution law. If the solution is sufficiently dilute and the degree of dissociation is small, activity coefficients tend to unity; if interionic attraction effects are also small the conductivity ratio, Λ_v/Λ_∞, can be used as an approximate measure of the degree of dissociation. Then $K = (\Lambda_v/\Lambda_\infty)^2c/(1 - \Lambda_v/\Lambda_\infty)$ or $c\Lambda_v = K(\Lambda_\infty^2/\Lambda_v) - K\Lambda_\infty$ and a plot of $c\Lambda_v$ (*i.e.*, 10^3 $\times$ specific conductivity) against Λ_v^{-1} should be a straight line of slope $K\Lambda_\infty^2$ and intercept $-K\Lambda_\infty$. A preliminary experiment showed that provided the halide concentration was $<1{\cdot}25 \times 10^{-3}$M the simple dilution law held. Conductivity data on triethyl-, tri*iso*propyl-, and triphenyl-tin chlorides at 25° ± 0·01° plotted in this way gave the following results (standard errors are given in parentheses):

R	Et	Pr^i	Ph
Λ_∞	34·7 (±1·9$_3$)	110 (±26)	303 (±91)
10^4K.....	1·12 (±0·13)	0·35$_1$ (±0·017)	0·0025$_3$ (±0·0015)
pK	3·95 (±0·05)	4·45$_3$ (±0·02)	6·60 (±0·26)

Potentiometric Measurements of Equilibria.—The e.m.f. at half-titration with silver nitrate of the halides R_3SnCl (R = Et, Pr^i, Bu^t, Ph) in 80% ethanol enables an estimate of their relative degrees of dissociation to be made. The titration was in acid solution (0·3M-perchloric acid) to suppress the dissociation of the ion $R_3SnOH_2^+$. The cell was made up as follows:

$$Ag \mid AgCl \mid R_3SnCl \text{ solution} \mid KNO_3(\text{satd.}) \mid KCl(\text{satd.}) \mid Hg_2Cl_2 \mid Hg$$

Measurements were made at 21° ± 0·1° with approximately 5×10^{-3}M-halide solutions.

For this cell, it being assumed that activity coefficients are unity because the solutions are dilute, we may write for its e.m.f., $E = \sum E_i + (\boldsymbol{RT/F}) \ln ([Ag^+]$, where $\sum E_i$ = the algebraic sum of liquid junction potentials, the potential of the reference electrode relative to hydrogen, and any asymmetry potential of the silver electrode arising from its previous history. The same cell is used for all the halides so that $\sum E_i$ is constant throughout the experiments. If the solubility product of silver chloride is K_s we have

$$E = \sum E_i - (\boldsymbol{RT/F}) \ln ([Cl^-]/K_s) \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Since water is in excess the equilibrium constant for the chloride hydrolysis is $K' = [R_3SnOH_2^+][Cl^-]/[R_3SnCl]$ and eqn. (1) then becomes

$$E = \text{const.} - (\boldsymbol{RT/F}) \ln K'[R_3SnCl]/[R_3SnOH_2^+]$$

At half-titration with silver ion $[R_3SnCl] = [R_3SnOH_2^+]$, and if $E_{\frac{1}{2}}$ is then the e.m.f. of the cell the difference between the $E_{\frac{1}{2}}$ values of any pair of halides (I) and (II) is $\Delta E_{\frac{1}{2}} = (\boldsymbol{RT}/\boldsymbol{F}) \ln (K'_{II}/K'_{I})$. The $E_{\frac{1}{2}}$ values for the halides R_3SnCl are as follows.

R	Et	Pr^i	Bu^t	Ph
$E_{\frac{1}{2}}$ (v)	0·04	0·06	0·17	0·065
K'_{Et}/K'_{R}	1	2·2	170	27

Discussion

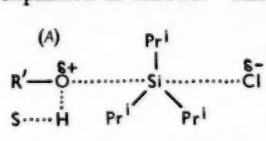
Kinetic Aspects.—Solvolysis of tri*iso*propyltin chloride with propan-2-ol is at a measurable rate: in water–dioxan, and in ethanol, equilibrium is established too rapidly for rate measurement and this is true also of the triethyl and triphenyl compounds in all solvents studied. In propan-2-ol solvolysis of the tri*iso*propyltin compound an unusual periodic change occurs in the observed conductivity which depends upon water concentration and temperature. The effect of water concentration makes it likely that the rapid initial increase in conductivity is caused by attack of water on the chloride. This increase is followed by a gradual decrease which may be due to the formation of another species of lower mobility, *e.g.*, the ion $Pr^i_3SnCl_2^-$, or to an electrochemical effect such as the formation of ion-pairs as the concentration of ions in the solution increases, or to a change in the conduction mechanism of the proton as water is removed from the solution by progressive reaction with chloride. At 0° there is finally another increase of conductivity which does not appear at 25°.

Two facts suggest that a synchronous type of substitution is occurring at tin: (*a*) measurable rates of solvolysis appear at R = Pr^i in the series R_3SnCl with R = Et, Pr^i, Bu^t in propan-2-ol and at R = Bu^t in ethanol; (*b*) solvolytic equilibria lie further in favour of the undissociated halide as the size and electron-releasing power of the alkyl group increase in this series. The converse of (*a*) and (*b*) would apply if solvolysis proceeded through a " stannonium " ion, R_3Sn^+. The solvolyses of *tert.*-butyl chloride in propan-2-ol show that only comparisons of rates in the same solvent are valid mechanistic criteria: thus, although the solvolysis rate (and degree of dissociation) of tri-*tert.*-butyltin chloride is lower in propan-2-ol than in ethanol this cannot be evidence that rearward attack is necessarily occurring at tin because the rate of solvolysis of *tert.*-butyl chloride, which reacts typically by the S_N1 mechanism, is also lower in propan-2-ol than in ethanol. This is an example of a specific solvent effect since the dielectric constants of the two alcohols are similar.

The characteristics of the solvolysis of tri*iso*propylsilyl chloride in propan-2-ol and propan-2-ol–water are clearly different from those of the corresponding tin compound. In hydrolysis, in the range of water concentration studied, a second-order reaction is observed which is not catalysed by pyridine: this is further evidence for a synchronous displacement process at silicon. The solvolysis by propan-2-ol–water has a low energy of activation and a very low steric factor which again is consistent with synchronous displacement.

Catalysis by pyridine in solvolysis rather than in hydrolysis in propan-2-ol may be explained as follows. The transition state is probably of the form [3] (*A*) in which S is a proton acceptor. In hydrolysis (R′ = H) it is probably as easy sterically for a propan-2-ol molecule to accept a proton as for a pyridine molecule: in solvolysis by propan-2-ol (R′ = Pr^i) catalysis would be expected if it is easier for a pyridine rather than a propan-2-ol molecule to approach the proton. Even if the steric requirements of the proton-transfer to pyridine and propan-2-ol are similar in the transition state, pyridine would be more effective in proton removal by virtue of its greater basic strength.

(A)



Kinetic data on silicon [3] and germanium [16] halides also indicate that R_3M^+ ions do not

[16] Johnson and Schmall, *J. Amer. Chem. Soc.*, 1958, **80**, 2931.

occur as intermediates in the solvolyses of these halides: the S_N1 mechanism is energetically unfavourable in the reactions of the halides R_3MCl of silicon, germanium, and tin.

Conductivity Data.—A necessary condition for dissociation of an organotin halide is the presence of a donor, S, the process being written $S: + R_3SnCl \rightleftharpoons {}^{+}S{:}SnR_3$ (I) $+ Cl^-$, where the species, I, may or may not undergo subsequent reaction, *e.g.*, proton transfer when S is hydroxylic. The extent of this subsequent reaction depends upon the nature of R and S. The extent of the dissociation depends upon S, and its dependence upon the medium is shown strikingly by the effect of water on the conductivity of tri*iso*propyltin chloride in dioxan: a 2×10^{-3}M-solution of the chloride does not conduct significantly until the water concentration reaches 2M. Not only must a donor molecule be present but the properties of the medium must be such as to promote dissociation: this medium effect could arise electrostatically or it could be a specific solvent effect.

In water–dioxan of constant composition (26% w/w of water; dielectric constant 15 [17]) some interesting features are shown when R is varied in R_3SnCl. The values of Λ_∞ (R = Et, 35; R = Pr^i, 110; R = Ph, 300) can be interpreted in terms of the properties of the corresponding hydroxy-compounds: Et_3SnOH is basic,[18] Pr^i_3SnOH only faintly so; [18] and Ph_3SnOH is acidic.[19] The dissociation constant of the acidic cation $R_3SnOH_2^+$ should therefore increase from ethyl to phenyl and this is reflected in the values of Λ_∞. That of the ethyl compound is typical for a 1 : 1 electrolyte with a large cation in a medium of this dielectric constant. Thus, interpolation of Kraus and Fuoss's data [20] on tetra*iso*-pentylammonium nitrate gives Λ_∞ 35·2, in satisfactory agreement with the value for triethyltin chloride in this medium. This confirms Dennison's finding [6] that in water triethyltin bromide behaved as a typical 1 : 1 electrolyte having Λ 112 ohm^{-1} cm.^{2}. If acid dissociation of the complex is substantial the high mobility of the proton should give a much larger value of Λ_∞. The Λ_∞ value for tri*iso*propyltin chloride shows that the acidic mode of dissociation makes a contribution, and in the triphenyl compound this appears to be considerable: this is consistent with the known basic propertes of the corresponding organotin hydroxides.

In propan-2-ol the relative values of the equivalent conductivity under the same conditions of temperature and concentration are:

$$\underset{100}{Pr^i_3SiCl} \gg \underset{3}{Et_3SnCl} > \underset{1}{Pr^i_3SnCl} > \underset{<0{\cdot}9}{Bu^t_3SnCl}$$

The value for Bu^t_3SnCl is maximal because the halide contained the dihalide as impurity. This emphasises a basic difference between the solvolysis of organosilyl chlorides and organotin chlorides ascribable to the differing extents of fission of the O–H bond in the scheme:

$$ROH + R_3MCl \rightleftharpoons R{-}\overset{+}{O}(H){-}MR_3 + Cl^-$$

Whereas when M is silicon, fission is essentially complete, when M is tin, fission is very limited.

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[17] Kraus and Fuoss, *J. Amer. Chem. Soc.*, 1933, **55**, 21.
[18] Luijten, personal communication.
[19] Swain, personal communication.
[20] Kraus and Fuoss, *J. Amer. Chem. Soc.*, 1957, **79**, 3301.

355. *Researches on Monolayers. Part VIII.*[1] *Reactions of Metal–Unsulphonated Ligand* (1 : 2) *Dyes with Protein and Similar Monolayers and their Relation to Dyeing Mechanisms.*

By C. H. Giles and T. H. MacEwan.

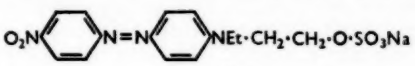
Dyes consisting of metal complexes with two unsulphonated azo-compounds as ligands have been applied to monolayers of edestin and methoxymethylnylon. The dyes are highly aggregated in the cold and their unusual effects on the films can be explained as due to adsorption as aggregates. The complexes have a dichelate structure. The aggregate, if ordered, must be a structure with " fins " of protruding aromatic nuclei, between which chain molecules in the film engage by non-polar, and in some cases polar, forces. A complex without pendant polar groups markedly increases film rigidity; proton-acceptor groups in a complex solubilise the films, and proton donor groups cross-link and stabilise them.

The mechanism of dyeing of nylon and protein fibres with these complexes is considered to be adsorption (probably of micelles), (*a*) in water-accessible regions by ion exchange, van der Waals forces, and, if suitable groups are available, hydrogen-bond donation by the dye to backbone –CO·NH– groups; and (*b*) in water-inaccessible regions, by van der Waals forces and by hydrogen bonding. Process (*b*) (" solid solution ") gives linear portions of adsorption isotherms.

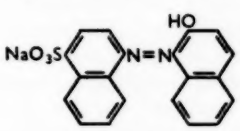
The 1 : 2-metal–ligand dyes, first introduced in 1949, are now important for colouring wool and synthetic fibres. They are anionic, being salts of strong acids, but they differ from the older 1 : 1-metal–ligand wool dyes in being unsulphonated and having their water-solubility conferred by non-ionic polar groups. They are distinguished by slow dyeing rate and very high fastness to wet treatments and to light, even in pale depths. A full account of their chemistry and development is given by Schetty.[2] Very little is known of their mechanism of dyeing; it must differ from that of most other wool dyes, which usually contain strongly ionic groups (generally SO_3Na). Schetty[2] considers that the dyeing process is similar to that of cellulose acetate with the non-ionic disperse dyes: the metal atom does not take part in the dye–fibre link, which is primarily due to van der Waals attraction. Zollinger[3] has obtained isotherms for two 1 : 2-complex dyes on several fibres and has interpreted them as evidence both of a " solid solution " mechanism, *i.e.*, similar to cellulose acetate dyeing, and of dye–fibre salt formation. Our results support the views of both these authors.

Part VII[1] described reactions of a protein (casein) in monolayers in presence of a variety of sulphonated dyes, etc. A similar technique was used here, with films of edestin and methoxymethylnylon and various solutes, including 1 : 2-complex dyes.

The following were used as models in studying the effect of the constitution of the solute upon the films: (I) D-glucose, (II) *meso*-inositol, (III) tannic acid, (IV) sodium



(VI)

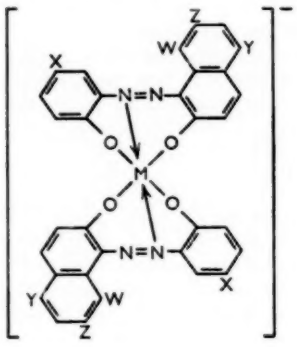


(VII)

1 : 2 : 4 : 5 : 6 : 8-hexahydroxyanthraquinone-3 : 7-disulphonate (Alizarine Cyanine; C.I. 58610), (V) tetradecyl sodium sulphate, (VI), and (VII) (C.I. 15620). Sodium salts of two

[1] Part VII, Cameron, Giles, and MacEwan, *J.*, 1958, 1224.
[2] Schetty, *J. Soc. Dyers Colourists*, 1955, **71**, 705.
[3] Zollinger, *Melliand Textilber.*, 1956, **37**, 1316; *Textil-Rundschau*, 1958, **13**, 217; cf. Back and Zollinger, *Helv. Chim. Acta*, 1958, **41**, 2242.

sulphonated azo-dye–chromium complexes (1 : 1) were included, *viz.*, (VIII) C.I. **13900**, complex of 3-amino-2-hydroxy-5-nitrobenzenesulphonic acid→acetoacetanilide, and (IX) C.I. **18745**, complex of 3-amino-2-hydroxy-5-nitrobenzenesulphonic acid→3-methyl-1-phenylpyrazol-5-one; and the sodium salts of the 1 : 2-metal–ligand dye anions (X)—(XV). Results are in Fig. 1.



Non-polar complex

(X) M = Cr; W, X, Y, Z = H

Proton-accepting polar complexes

(XI) M = Cr; X = SO_2Me; W, Y, Z = H
(XII) M = Co; X = SO_2Me; W, Y, Z = H

Proton-donating polar complexes

(XIII) M = Cr; W = NH·COMe; X = SO_2Me; Y, Z = H
(XIV) M = Cr; X = SO_2Me; Y = NH·COMe; W, Z = H
(XV) M = Cr; W, X, Y = H; Z = OH

Experimental

Apparatus and experimental details were described previously.[1] The dyes were chromatographically pure and contained only a few % of inorganic salt, which exerts no influence under buffer conditions. Edestin was a commercial sample (B.D.H.) spread from a 0·1% solution in 0·5M-sodium hydroxide. Methoxymethylnylon (Imperial Chemical Industries Limited; 40% methoxymethyl substitution in amide group of nylon 66) was spread from a 0·01% solution in methanol. Qualitative viscosity tests to confirm rigidity were made by blowing on the films after covering them with talc.

According to Fosbinder and Lessig[4] edestin only spreads on substrates above or below pH 5·0—11·0. We used pH 2·3—4·7. In all cases the spreading was spontaneous and the films were quite stable.

Fading tests were made as follows: formaldehyde-hardened gelatin films[5] dyed with dyes (X), (XI), or (XIII) by placing them in 10^{-5}M-solutions at 40° for *ca.* 2 hr. and then leaving overnight in the cooling solution, were rinsed, and then dried in air. They were then exposed 8 in. from a 400 w mercury-vapour lamp (cf. ref. 5). The optical density of each film was measured before and at intervals during exposure on a Unicam S.P. 600 spectrophotometer, in the waveband of maximum absorption (which was not sharp). Change in temperature and time of dyeing did not significantly alter fading characteristics.

Discussion

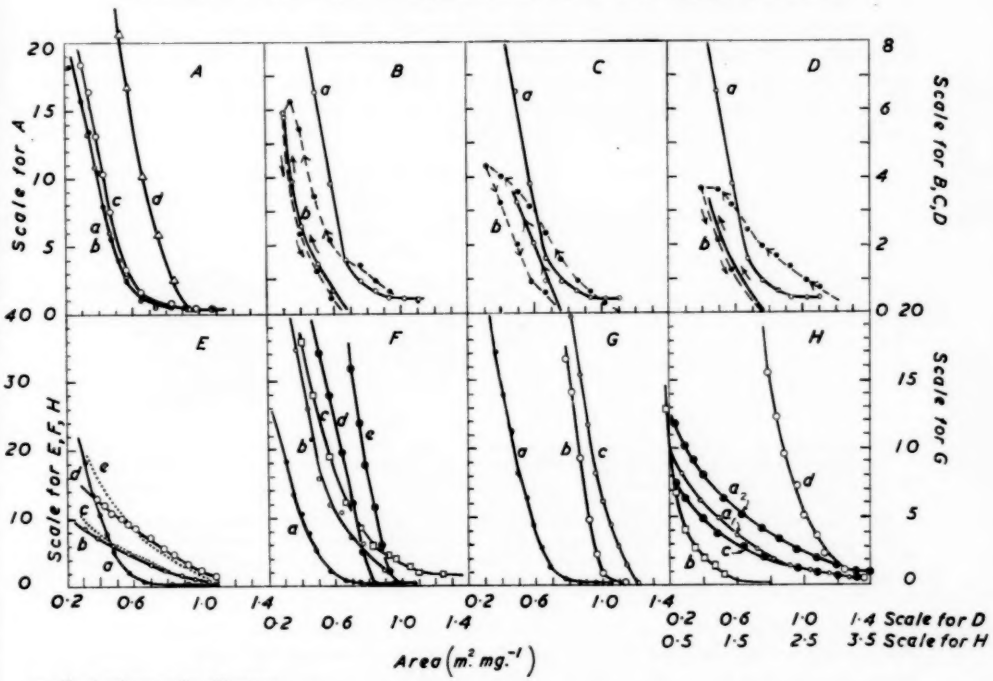
The previous results[1] were considered as evidence that (*a*) Monobasic compounds of weak hydrogen-bonding power at high film pressures tend to form a duplex layer or a layer of micelles beneath the film, which thus becomes more soluble (but see below); (*b*) Solutes with two sulphonate groups expand the film slightly through cross-linking by ion–ion attraction; (*c*) Bifunctional hydrogen-bond donating compounds cause film "condensation" (especially noticeable with Alizarine Cyanine). The present results are interpreted on the following basis; a fall in the slope of the curve shows that the film solubility increases; a rise in slope coupled with increase in rigidity of the film, demonstrated by the powder test, shows that cross-linking has occurred.

Effects produced by Hydroxylic Solutes.—Glucose appears not to form bonds with proteins in water, and has no effect on the film (Fig. 1*A*, *b*), but *meso*-inositol does form complexes (detected by refractometry)[6] and it also appears to have a small cross-linking

[4] Fosbinder and Lessig, *J. Franklin Inst.*, 1933, **215**, 579.
[5] Baxter, Giles, and Lewington, *J. Soc. Dyers Colourists*, 1957, **73**, 386.
[6] Bruce, Giles, and Jain, *J.*, 1958, 1610.

effect in the film (Fig. 1*A*, *c*). (The difference between these two solutes is attributable to differences in attraction for water, reflected in their solubilities [6].) Tannic acid makes the methoxymethylnylon film very rigid; so does, in less degree, Alizarine Cyanine (IV). In view of the conclusions to be discussed regarding the 1 : 2-complexes, it is possible that this dye may be adsorbed as a micelle; it is rather insoluble. These results are consistent with earlier observations on the effects of hydroxylic molecules. Thus Ellis and Pankhurst [7a] (cf. ref. 7*b*) observed that collagen films were not " condensed " by monomeric mono-, di-, and tri-hydric phenols, but only by polyhydric phenols of molecular weight higher than the catechin monomer; Clark, Holt, and Went [8] found that nylon or protein films are " condensed " by silicic acid only after the latter has polymerised. In both those cases the condensation takes place through film–solute hydrogen bonding.

FIG. 1. *Force–area curves for edestin films (A—G) and methoxymethylnylon films (H).*



a: Control curve in all cases.
A: *b* (coinciding with *a*), (I), 10^{-2}M; *c*, (II), 10^{-2}M; *d*, (IV), 5×10^{-4}M. All at pH 2·30.
B: *b*, (V), 5×10^{-5}M, showing first compression, expansion, and second compression (pH 2·30).
C: *b*, (VI), 10^{-4}M, as *B*,*b* (pH 2·30).
D: *b*, (VII), 10^{-4}M, as *B*,*b* (pH 2·30).
E: *b*, (XI), 10^{-5}M; *c*, (VIII), 10^{-4}M; *d*, (XII), 10^{-5}M; *e*, (IX), 10^{-4}M. All at pH 3·26.
F: *b*, (XIV), 10^{-5}M; *c*, (XIII), 10^{-5}M; *d*, (XV), 10^{-5}M; *e*, (X), 10^{-5}M. All at pH 3·26.
G: *b*, (XV), 10^{-5}M; *c*, (X), 10^{-5}M. Both at pH 4·70.
H: a_1, control at pH 3·26; a_2 control at pH 1·60; *b*, (III), 40 mg. l.$^{-1}$ at pH 1·60; *c*, (IV), 5×10^{-4}M at pH 1·60; *d*, (X), 10^{-4}M at pH 3·26.

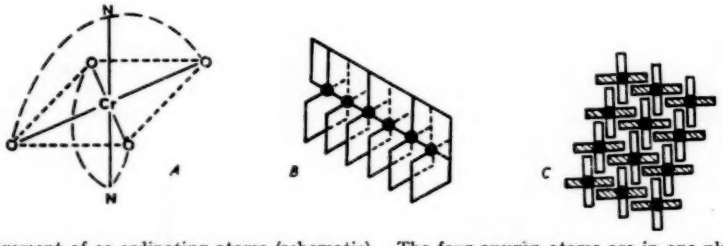
Effects produced by Sulphate Esters and Monosulphonated Dyes.—The effect of the surface-active dyes (VI)—(IX) on edestin films (Fig. 1*C*, 1*D*, 1*E*, *c* and *e*) resembles their effect on casein films [1] and a similar explanation may be offered, *viz.*, film penetration at

[7] (*a*) Ellis and Pankhurst, *Discuss. Faraday Soc.*, 1954, **16**, 170; (*b*) Lanham and Pankhurst, *Trans. Faraday Soc.*, 1956, **52**, 521.
[8] Clark, Holt, and Went, *Trans. Faraday Soc.*, 1957, **53**, 1500; Clark and Holt, *ibid.*, p. 1509.

low pressures, and at high pressures some adsorption of a duplex film or micelles below the surface (though there may also be some penetration to give a mixed monolayer). Decompression followed by recompression showed that edestin films on solutions of the surface-active compounds (V)—(IX) were unstable during first compression, apparently through slow dissolution (casein films do not behave thus; see Experimental section of ref. 1). They were stable when subsequently expanded and recompressed, provided they were allowed to stand for 30 min. between each reading during the recompression cycle (see Fig. 1*B*—1*D*, *b*). The recompression curves may represent some form of more stable duplex layers (cf. Fig. 11*a* of ref. 9, though it seems more likely that in the present films the top layer is protein).

Effects produced by 1 : 2-*Complex Dyes.*—Dye (X), which has no available polar groups, surprisingly causes an extreme increase in rigidity of the film (Fig. 1*F*, *e*), of a magnitude previously only observed with solutes with large, polymeric molecules containing powerfully proton-donating groups, *e.g.*, tannic acid (cf. ref. 7); the addition of such groups, as in (XIII)—(XV) (Fig. 1*F*, *b*, *c*, *d*), slightly *reduces* rigidity [at pH 3·26; at pH 4·7 (XV) slightly *increases* rigidity]. Further, dyes (XI) and (XII) (Fig. 1*E*, *b*, *d*) are even more effective than normal surface-active dyes (VI, VII, cf. XII of ref. 1) (Fig. 1*E*, *b*, *d*) in making the films compressible, yet they are not surface active. (None of these 1 : 2-complexes

FIG. 2. *Structure of* 1 : 2-*metal–ligand dye molecule and micelle.*



A. Arrangement of co-ordinating atoms (schematic). The four oxygen atoms are in one plane. The curved broken lines show the three chelating atoms of the respective azo-dye molecules.
B. Isometric projection (schematic) of one line of associated complex molecules in suggested micelle. (Azo-dye units are shown as plain rectangles for clarity.)
C. Plan (schematic) of one part of a layer of suggested micelle, showing interlocking of azo-dye units by planar association. Hatched rectangles show units below, and white rectangles show units above, the line of metal atoms. Dimensions of unit cross-sections and metal atoms approximately to scale. [Dye (X), close-packed micelle; dyes with bulky peripheral polar groups may have a less close-packed structure.]

gave any evidence of surface activity.) The most reasonable interpretation of these phenomena, consistent with other properties of the dyes, is that the adsorbed species is in all cases a dye micelle. This is best discussed with reference first to the geometry of these dye molecules.

Nature of the 1 : 2-*Complex Dye Micelle.*—These dyes are not generally very soluble in water and are highly aggregated in the cold [2] [some of the present examples slowly flocculated and (X) was particularly insoluble (*ca.* 10^{-5}M in acid solutions)]. In attempting to interpret their adsorption behaviour we must consider the probable structure of the dye aggregates. As far as we know, micelles of dichelate compounds have not been studied, but those of long paraffin-chain ions in water have received considerable attention. In these there is an equilibrium between the short-range van der Waals forces, which bring the hydrocarbon chains into contact, thus expelling them from the water, and the long-range coulombic forces which cause mutual repulsion of the ionic groups.[10] In micelles of large planar anionic azo-dye molecules in water [11] and in monolayers of planar azo-dyes on

[9] Matalon and Schulman, *Discuss. Faraday Soc.*, 1949, **6**, 27.
[10] Tartar, *J. Phys. Chem.*, 1955, **59**, 1195.
[11] Morton, *J. Soc. Dyers Colourists*, 1946, **62**, 272.

water [12] the aromatic nuclei appear to be stacked side-by-side; thus there is the closest contact of the hydrocarbon portions. In the present case we assume (*a*) that the micelles have an ordered structure and (*b*) that this structure is determined by the tendency of the short-range forces to promote the closest possible contact between the planar dye units of adjacent molecules. On these assumptions, molecular models show that the aggregate must have an unusual structure. The model shows that the four oxygen atoms of the *o*-hydroxy-groups in the complex lie in one plane, with the respective co-ordinated nitrogen atoms of the two azo-groups arranged perpendicularly to this plane and equidistant from all the oxygen atoms. The two azo-dye units in the complex are planar and lie at right-angles to each other (cf. ref. 13) (see Fig. 2*A*), giving a dichelate-type of molecule. The principal aggregating force is assumed to be the tendency of the hydrophobic portions of

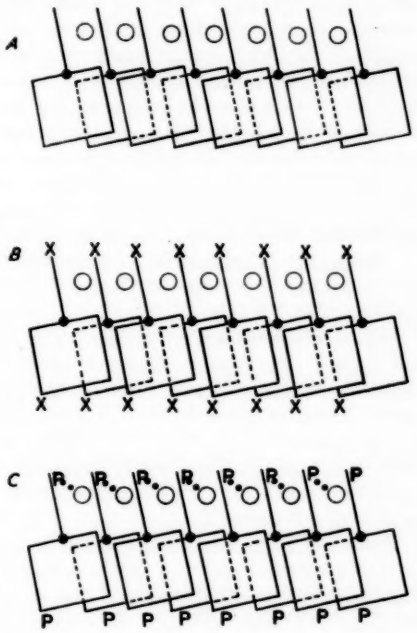


FIG. 3. *Schematic representation of possible mode of film–dye micelle association. Film chain molecules* (○) *orientated perpendicular to the paper. For clarity, dye units are shown as rectangles (face-on) and lines (edge-on), and tilted.*

A. Adsorption of non-polar dye (X).
B. Adsorption of dyes (XI) and (XII) at high film pressures. Proton-acceptor groups **X** beneath the micelle confer high solubility.
C. Adsorption of dyes (XIII)—(XV). Proton-donor groups *P* bond with film chains above micelle, and with water below.

these planar units to escape from the water and achieve closest side-by-side contact with neighbouring units. Models show that apparently the only way in which this can occur is in the form of structure illustrated in Fig. 2*B*, 2*C*, which is the most closely-packed possible arrangement. This structure can clearly be elaborated in three dimensions. The gegenions (usually sodium) may be accommodated partly in the gaps inside the structure and partly in the surrounding solution. Stability is enhanced by the wide separation of the ionic centres.

Nature of Micelle–Film Bonds.—A study of the suggested micellar structure (Fig. 2*B*, 2*C*) shows that (i) its external surface consists of planar dye units protruding as a series of " fins " and (ii) protein or other linear polymer chains can stretch across the surface in parallel lines, held between the " fins," whether these have small pendant polar groups or not (Fig. 3*A*). (There are narrow, parallel straight channels across the surface [of the micelle, dye (X)], but wider ones could be followed by the film chains if these are bent or helical.) In the absence of polar groups on the dye units non-polar forces must hold the

[12] Giles and Neustädter, *J.*, 1952, 3806; Cameron and Giles, *J.*, 1957, 3140.
[13] Race, Rowe, and Speakman, *J. Soc. Dyers Colourists*, 1946, **62**, 372.

protein or nylon backbones in these channels, the whole forming a rigid two-dimensional network. Thus this structure can account for the observed rigidity produced by dye (X), which has no available polar groups and if monodisperse would not be expected to have any such effect. In the structure actually shown in Fig. 2*C*, adsorbed protein backbone chains would be nearly twice as far apart as when close-packed alone on the surface. The actual increase in area observed with (X) is about 80%. The micelle structure also accounts for the effects of the other 1 : 2-complexes as follows.

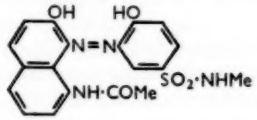
(i) The micelles of (XI) and (XII) have an exterior surface exposing strongly polar, water-attracting proton-accepting groups (SO_2Me) (Fig. 3*B*). Models show that the micelle can tilt to give an upper hydrophobic and a lower hydrophilic surface. If adsorbed that way the under-surface of the film–dye micelle assembly would be water-soluble, which would explain why the whole film shows the force–area curve characteristic of normal surface-active dye–protein films, with very high compressibility. (Proton-accepting groups do not form strong bonds with proteins.[1,14,15])

(ii) The films with dyes (XIII)—(XV) also have strongly water-attracting under-surfaces. Their effect in increasing the film solubility (Fig. 1*F*, 1*G*) is however masked by the competitive action of the polar groups in the upper surfaces of the micelles. These groups are strongly proton-donating and form stable hydrogen-bond cross-links with the protein chains. The result is that these dyes do increase the rigidity of the film considerably, but a little less so than does the non-polar dye (X), and they increase the film area less than (X) does, probably because of their stronger cross-linking action.

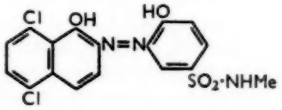
Change in pH from 3·26 to 4·7 has no effect on the increase in edestin film area produced by the proton-donor dye (XV), but it slightly reduces (by *ca.* 5%) the increase given by the non-polar dye (X).

Effect of Chelation in Complex.—The acetamido-group in (XIII) is chelated with the azo-group.[2] The dye is thus not normally a proton-donor. This explains its marked expansive and solubilising effect on edestin films below 10 dynes cm.$^{-1}$ (Fig. 1*F*, 1*C*). At higher pressures however the dye causes marked film rigidity and so must then be acting as a proton-donor [cf. (XIV), (XV), Fig. 1*F*, *b*, *d*]; when the complex molecules are forced close to the protein the chelate ring presumably breaks and a dye–protein hydrogen bond forms preferentially. This is consistent with the known weakness of a second hydrogen bond to an azo-group.[12]

Nature of Film–Dye Hydrogen Bonds.—The proton-donor dye (IV) has much less effect on the compressibility of methoxymethyl nylon films (Fig. 1*H*, *c*) than on edestin (Fig. 1*A*, *d*); the hydrogen-bond acceptor centres in the films are therefore probably the backbone –CO·NH– groups. In contrast, the non-polar dye (X) has a similar effect on both films (Fig. 1*F*, *e* and 1*H*, *d*), confirming non-hydrogen-bond adsorption. Earlier adsorption tests[14,15] showed that some proton-donors are much more strongly adsorbed than proton-acceptors by protein or nylon fibres, from solutions or as vapours. The solutes used now and previously show the same effect. In ability to bind with proteins or nylon, groups fall roughly thus: ArOH > Ar·NH·COMe > Ar·NH_2, Ar·NHR, Alk–OH > proton-acceptor groups.



(XVI)



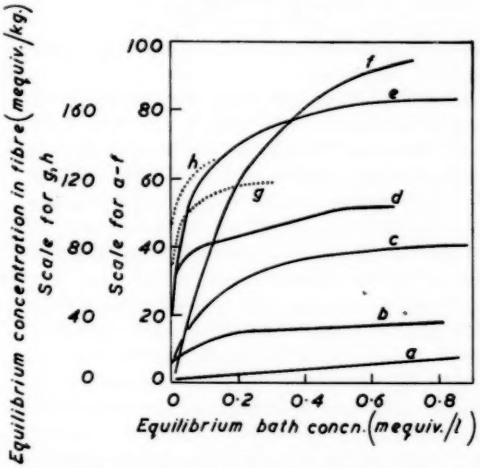
(XVII)

Isotherms for Adsorption by Fibres.—Zollinger[3] postulated salt-formation and solid solution of the free acid form to account for the isotherms he obtained, shown in Fig. 4, for

[14] Chipalkatti, Giles, and Vallance, *J.*, 1954, 4375.
[15] Chipalkatti (H. R.), Chipalkatti (V. B.), and Giles, *J. Soc. Dyers Colourists*, 1955, **71**, 652.

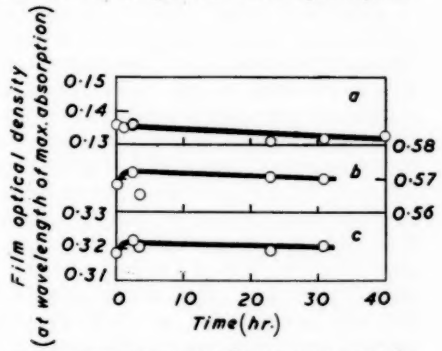
2 : 1 ligand–chromium complexes of (XVI) and (XVII). This interpretation is now confirmed, and may be extended in the light of present and other work (*e.g.*, refs.[1,7,8,16,17]) as follows. Normal (L type [16]) curves for silk (Fig. 4, *c*) and wool (*f*) represent mainly ion-exchange adsorption in *water-accessible* regions of the fibres. Linear portions of curves, for acetylated wool (*a*), acetylated nylon (*b*, very low slope), and stretched nylon (*d*) represent mainly hydrogen-bond adsorption in *water-inaccessible* regions.[16] [Acetylation removes the ion-exchange centres ($^+NH_3$ groups) in the fibre.] All the curves for nylon (*b*, *d*, *e*, *g*, *h*), unlike those for silk and wool, have " high affinity "[16] character, *i.e.*, initially they coincide with the *y*-axis. There is therefore a source of high affinity in nylon which

FIG. 4. *Adsorption isotherms of* 1 : 2*-metal–ligand dyes (after Zollinger* [3]).



Dye (XVI): *a*, Acetylated wool; *b*, acetylated nylon 66; *c*, silk; *d*, stretched nylon 66; *e*, unstretched nylon 66; *f*, wool.
Dye (XVII): *g*, acetylated nylon 66; *h*, stretched nylon 66.

FIG. 5. *Rates of photo-degradation of unsulphonated dye–metal complexes adsorbed in gelatin films.*



a, (X), measured at 5600 Å; *b*,* (XI), 4700 Å; *c*,* (XIII), 6200 Å.

* Slight increases in optical density in initial stages of irradiation, as shown here, have been observed in other cases with particulate colouring matters, and are attributed to breakdown of some particles into smaller units in the heat of the lamp (see ref. 5).

is not present in the proteins; this source must be van der Waals attraction by the hydrocarbon portions of the nylon chains; very possibly this high affinity arises from the engagement of the chains with the dye micelle [cf. Fig. 3*A* and the strong adsorption of (X) to the films]. Other work shows that " high-affinity " curves are almost always due to micellar adsorption.

In unstretched nylon all the regions of the fibre accessible to dye are accessible to water (the isotherm has no linear portion). In the stretched fibre there are regions accessible to dye but not to water (the isotherm has a linear portion).

Dye (XVII) has higher non-polar attraction than (XVI) for nylon; this follows from these considerations: (i) adsorption of (XVII) is higher on both forms of nylon (Fig. 4, *g*, *b*, *h*, *d*); (ii) a lower proportion of the total adsorption of (XVII) than of that of (XVI) is due to ion-exchange, since acetylation reduces adsorption of (XVII) much less than (XVI) (Fig. 4, *h*, *g*; *d*, *b*); (iii) the non-linear isotherms indicate adsorption in water-accessible regions, in which (XVII), not being a proton-donor, has low hydrogen-bond affinity.

[16] Giles and MacEwan, *Proc. 2nd Internat. Congr. Surface Activity*, 1957, **3**, 457.
[17] Cameron, Giles, and MacEwan, *J.*, 1957, 4304.

Therefore, the main affinity of (XVII) must be non-polar (probably van der Waals attraction between the planar dye molecules and the hydrocarbon portions of the nylon molecular chain).

Models give evidence of a possible reason for the affinity difference between (XVI) and (XVII). Thus: (*a*) the longest molecular axis parallel with the micelle surface (*i.e.*, length of " fin ") is longer in (XVII) (*ca.* 14·5 Å) than in (XVI) (*ca.* 12 Å). (*b*) The NH·COMe substituent in (XVI) may interfere sterically with penetration of the nylon chain between the " fins." Both effects (*a*) and (*b*) will tend to reduce the area of direct contact of dye and fibre molecule, and thus will reduce their mutual van der Waals attraction.

Micellar Adsorption.—The properties of these dyes in fibres are consistent with their presence as large micelles of fairly uniform size. Dyeing is normally carried out at the b. p., and under these conditions the dyes have low degrees of aggregation.[2] Dye molecules entering the fibre may therefore be nearly monodisperse. Aggregates must then build up on the internal fibre surfaces, probably during dyeing, but possibly during subsequent cooling or drying.

Light Fastness of 1 : 2-*Metal–Ligand Dyes.*—Schetty [2] reports that a noticeable difference between the (Irgalan) 1 : 2-metal complex dyes and ordinary acid wool dyes " is that the former show within narrow limits constant light fastness when applied to the most diverse substances, such as silk, wool, nylon, Perlon, acetate rayon, and lacquers." Large aggregates of dye fade much more slowly than monodisperse dye molecules.[18] The micellar structure of these dyes postulated here would be expected to persist in all media (aqueous or non-aqueous) because of the high mutual attraction of the planar aromatic nuclei; and if it does, the consistently high resistance to light of these substances is explained.

Experiment has shown that dyes in monodisperse form fade approximately at a first-order rate, *i.e.*, exponentially, but when they are entirely in aggregates, *e.g.*, insoluble pigments, they fade at a steady rate (zero order), indicative of fading at the outer surface only of particles.[5] Most normal soluble dyes in transparent substrates, *e.g.*, gelatin, at first fade exponentially, and then, after a small proportion (*ca.* 10%) has been destroyed, the rate becomes steady.[18] This behaviour indicates the presence of a little monodisperse dye, which fades first, and some associated dye, which fades more slowly. Thus a fading-rate test can give useful information of the physical state of adsorbed dye. Fading tests were therefore made in this investigation as a check on the hypothesis that the 1 : 2-complex dyes are adsorbed mainly as micelles. The results are shown in Fig. 5. There is no evidence of an initial rapid loss in optical density, and this is consistent with a very large proportion of the adsorbed dye being in micellar form.

Mechanism of Dyeing.—All the facts suggest the following tentative picture of the dyeing mechanism on nylon and protein fibres. The dye builds up in the fibre during dyeing (probably) or subsequently, as " network " micelles (Fig. 2*B*, 2*C*). The adsorption mechanisms are: (a) *in water-accessible* regions of the fibre: (i) ion-exchange of the dye sodium salt with cationic amino-groups in both types of fibre, (ii) van der Waals attraction between the hydrocarbon parts of the nylon (and perhaps the protein) chain and (probably) the aromatic residues at the surface of the dye micelles, (iii) hydrogen-bond donation by the dye (if suitable groups are present) with backbone –CO·NH– groups in the fibre; (b) in *water-inaccessible* regions the free acid may be adsorbed preferentially by both mechanism (ii) and (iii) and also by hydrogen-bond acceptance by the dye.

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[*Received, August 28th,* 1958.]

[18] Giles, *J. Soc. Dyers Colourists*, 1957, **73**, 127.

356. *A Quantitative Study of Homolytic Methylation of Some Monosubstituted Benzenes.*

By B. R. Cowley, R. O. C. Norman, and William A. Waters.

Di-*tert.*-butyl peroxide has been decomposed in hot solutions of chlorobenzene, bromobenzene, nitrobenzene, anisole, and benzonitrile. The products have been separated by distillation and the resulting mixtures of substituted toluenes analysed by vapour-phase chromatography and infrared spectroscopy.

The isomer ratios for methylation resemble, in general, those published for phenylation, but some consistent differences indicated that methyl are more nucleophilic than phenyl radicals.

Comprehensive researches by Hey and his colleagues and by workers in other countries have yielded quantitative information concerning isomer ratios and partial rate factors for the homolytic phenylation of monosubstituted benzenes.[1] Significant features are (i) the prevalence of a high proportion of *ortho*-substituted product, except when steric hindrance is a deterring factor, and (ii) a tendency for the *meta* : *para* ratio to fall below the statistical figure of two for all substituent groups. However, when substituted phenyl radicals are used in place of phenyl itself, the *meta* : *para* ratios change in a way that consistently indicates that free neutral radicals can exhibit dipolar character.[2]

Substantially the same conclusions concerning the dipolar character of free radicals have been reached from studies of free alkyl radicals produced by oxidations involving one-electron transfer.[3] Methyl should be nucleophilic rather than electrophilic since the tendency for electron loss (E_{-e}) by the transfer $\cdot CH_3 \longrightarrow (CH_3^+) + e$ is greater than that for electron gain (E_{+e}) by the process $e + \cdot CH_3 \longrightarrow (:CH_3^-)$.

The greater electronegativity of sp^2- than of sp^3-carbon suggests that the methyl radical might lose an electron somewhat more easily than the phenyl radical does, but the difference in electronegativities is small, and there should only be a slight difference between the dipolar characters of the two radicals. Direct comparison between the actions of free methyl and free phenyl radicals in aromatic substitution is thus theoretically important, but the reactivity of simple benzene derivatives with free methyl is so low that until recently the occurrence of nuclear methylation could only be deduced inferentially from the examination of other reaction products, *e.g.*, methylated diaryls produced from the decomposition of di-*tert.*-butyl peroxide in boiling chlorobenzene,[4] or the gaseous products resulting from decomposition of acetyl peroxide in solution in substituted benzenes.[5] However, new techniques (see below) have given reproducible isomer ratios (Table 1) for direct methylation of chlorobenzene, bromobenzene, nitrobenzene, anisole, and benzonitrile by methyl radicals generated by thermal decomposition of dilute solutions of di-*tert.*-butyl peroxide.

In these experiments the big excess of unchanged starting material was removed by slow fractional distillation, vapour-phase chromatography showing that no product was removed therein. Vapour-phase chromatography was also used for analysis of the products; *o*-, *m*-, and *p*-nitrotoluene were quantitatively resolved, with 2 : 4 : 7-trinitrofluorenone as the stationary phase;[6] in other cases the mixture of methylated isomers was separated from other products by collecting the fraction eluted from the column after the appropriate retention time and subjected to infrared analysis. Confirmatory experiments

[1] Augood and Williams, *Chem. Rev.*, 1957, **57**, 123.
[2] Dannley and Sternfeld, *J. Amer. Chem. Soc.*, 1954, **76**, 4543; DeTar and Kazimi, *ibid.*, 1955, **77**, 3842; Cadogan, Hey, and Williams, *J.*, 1955, 1425; Shih, Hey, and Williams, *J.*, 1958, 1885.
[3] Mackinnon and Waters, *J.*, 1953, 323.
[4] Beckwith and Waters, *J.*, 1957, 1665.
[5] Heilman, Rembaum, and Szwarc, *J.*, 1957, 1128.
[6] Norman, *Proc. Chem. Soc.*, 1958, 151.

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showed that the mixture of isomers could be collected without preferential loss. Our results are in Table 1, with the data of Eliel *et al.*[7] for the methylation of toluene.

TABLE 1. *Percentages of* ortho-, meta-, *and* para-*isomers obtained by free-radical methylation.*

	Methyl derivative					Methyl derivative			
Compound	*ortho*	*meta*	*para*	Temp.	Compound	*ortho*	*meta*	*para*	Temp.
PhCl	64	25	11	130°	$PhNO_2$	65·5	6	28·5	143°
PhBr	67·5	23	9·5	145	PhCN	48	9	43	133
PhOMe	74	15	11	140	PhMe	56·5	26·5	17	110

Whilst all the methylations produced involatile polymeric material, *e.g.*, aryl coupling products, dimethylation was insignificant with the dilute solutions of di-*tert.*-butyl peroxide used. Anisole, however, yielded a small quantity of free phenol (Kharasch and Huang [8] have shown that many phenol ethers, though not anisole itself, can be dealkylated by free radicals at a much lower temperature than that of our experiments).

Benzonitrile has an unexpectedly high methyl affinity,[5] which is consistent with the occurrence of the addition of methyl radicals to the C≡N group; and phenyl-radical attack on the carbon atom of the cyano-group is known; but although products from the addition of methyl radicals to the cyano-group were searched for, none could be detected. With nitrobenzene, side reactions involving the nitro-group probably occur, since the reaction mixture rapidly darkens; this is not the case with the aryl halides.

Although total rate factors for methylation of benzene derivatives are available from work by Heilman *et al.*,[5] it is impossible to obtain accurate partial rate factors by combining these total rate factors with our isomer ratios, since the two sets of experiments were conducted at different temperatures and it is known that isomer ratios can change considerably over a 100° temperature range.[10] An attempt was made to establish a new scale of total rate factors by comparing the overall extent of methylation of chlorobenzene with that of benzene, but because of the low reactivity of benzene the molar ratio benzene : chlorobenzene had to be high to give sufficient reaction for quantitative measurement; this caused the reflux temperature to be too low for sufficient methylation to occur.

Differences between phenylation and methylation can be discussed in terms of isomer ratios. Table 2*A* lists percentages of *ortho*-substitution for both groups, and Table 2*B* lists *meta* : *para* ratios.

TABLE 2.

Compound	PhMe	PhCl	PhBr	PhOMe	$PhNO_2$	PhCN *
		(*A*) *Ortho* (%)				
Phenylation	71	62	49	67	62·5	60
Temp.	80°	80°	80°		80°	
Methylation	56·5	64	67·5	74	65·5	48
Temp.	110°	130°	145°	140°	143°	133°
		(*B*) *Meta* : *para* ratio				
Phenylation	1·32	1·71	1·91	1·20	0·36	0·33
Methylation	1·56	2·27	2·42	1·36	0·21	0·21

* Approximate values.

Substitution by both phenyl and methyl occurs predominantly in the *ortho*-position; the somewhat higher figures for methylation, especially with bromobenzene, possibly indicate slightly less steric hindrance to methylation than to phenylation. If so, however, the figures [7] for methylation of toluene at 110° are anomalous, for a higher *ortho* : *para* ratio would be expected.

A slight, but clear, polar difference between phenyl and methyl radicals is evident here.

[7] Eliel, Rabindran, and Wilen, *J. Org. Chem.*, 1957, **22**, 859.
[8] Kharasch and Huang, *ibid.*, 1952, **17**, 669.
[9] Hanby and Waters, *J.*, 1939, 1792.
[10] Cf. Kent and Norman, *J.*, 1959, 1724.

Considering substituents in groups according to their known directive actions in heterolytic electrophilic substitution, we can see that for *ortho-para*-directing substituents the *meta* : *para* ratio is invariably higher for homolytic methylation than for phenylation; whilst with the two substituents of opposite directive character, nitro and cyano, the *meta* : *para* ratio is lower for methylation than for phenylation. Now, *meta*-substitution of a compound such as toluene, and, still more, *para*-substitution of a compound such as nitrobenzene, is characteristic of nucleophilic substitution, *i.e.*, attack by a group which can donate electrons to the aromatic ring. Thus, in homolytic aromatic substitution the methyl radical shows the same tendency to electron loss that is exhibited by other alkyl radicals, and a greater tendency to such electron loss than is exhibited by the phenyl radical. It is possible, then, for homolytic aromatic substitution, to write an order of increasing electrophilicity, based on this and other work,[2] in which methyl can now be included, as follows: $Me < Ph < C_6H_4Cl$, $C_6H_4{\cdot}NO_2$.

Experimental

Reaction of Methyl Radicals with Chlorobenzene.—Di-*tert.*-butyl peroxide (13 g.) and purified chlorobenzene (100 ml.) were refluxed together for 72 hr. The temperature was kept near 130° by removing the *tert.*-butyl alcohol and acetone as formed. The remaining low-boiling products and most of the unchanged chlorobenzene (*ca.* 80 ml.) were removed through a fractionating column, and the residue fractionally distilled into fractions, (*a*) b. p. 40—42°/30 mm., (*b*) b. p. 50—70°/30 mm., (*c*) a tarry residue.

Fractions (*a*) and (*b*) were examined by vapour-phase chromatography on a column (450 cm. × 9 mm.) packed with I.C.I. E 301 silicone rubber (20 parts) coated on 30—40 mesh " Sil-o-cel " firebrick (80 parts). The column was operated at 170° at atmospheric pressure with a carrying stream of nitrogen (100 ml./min.), and the material eluted was detected with a conductivity cell. Fraction (*a*) gave one peak only, with a retention time of 19½ min., the same as that of chlorobenzene. Fraction (*b*) gave two peaks: one with a retention time of 19½ min. (chlorobenzene), the other, much weaker, with a retention time of 24 min. A mixture of equal parts of *o*-, *m*-, and *p*-chlorotoluene gave one peak only, with retention time 24 min.; no resolution of the three isomers was observed. Repeated injections of 0·1 ml. samples of fraction (*b*) coupled with collection of the chlorotoluene fraction yielded sufficient material for determination, by infrared spectroscopy, of the proportions of the three isomers present.

Reaction of Methyl Radicals with Bromobenzene.—Di-*tert.*-butyl peroxide (13 g.) and purified bromobenzene (100 ml.) were refluxed together for 32 hr., the temperature being kept at about 145° as above. The low-boiling products and about 75 ml. of unchanged bromobenzene were removed by fractionation, and the fraction of the residue boiling below 90°/13 mm. was examined by vapour-phase chromatography on the column described above, operated at 180° at atmospheric pressure with a carrying stream of nitrogen (30 ml./min.). Injection of a 0·03 ml. sample gave an intense peak with retention time 16 min. and a weaker peak with retention time 24 min., due respectively to bromobenzene and bromotoluenes, the bromotoluene peak not being resolved. A sample of the bromotoluenes was collected and analysed spectroscopically.

Reaction of Methyl Radicals with Anisole.—Di-*tert.*-butyl peroxide (13 g.) and purified anisole (100 ml.) were refluxed together for 40 hr., the temperature being kept at about 140° as above. The low-boiling products and about 75 ml. of the unchanged anisole were removed by fractionation, vapour-phase chromatography of the distillate showing that no methyl tolyl ethers were present. The fraction of the residue boiling below 200° was examined by vapour-phase chromatography on the column described above and in the conditions of the bromobenzene experiment. Injection of a 0·03 ml. sample gave an intense peak with retention time 17½ min. and a small peak with retention time 27 min., these being shown by comparison with authentic materials to be due respectively to anisole and the methyl tolyl ethers, these isomers not being resolved. A sample of the mixed methyl tolyl ethers was collected for analysis.

Injection of a larger (0·2 ml.) sample of the distillate gave a further small peak with retention time 22 min.; the material responsible for this peak was collected and was shown by its infrared spectrum to be phenol. The residue from a fractionated sample of the anisole used in these experiments was shown by vapour-phase chromatography not to contain phenol.

Spectroscopic Analysis.—Determinations were carried out with a Perkin-Elmer Recording infrared spectrophotometer (Model 21). Investigations in the 12—14 μ region for solutions of the pure chlorotoluenes, bromotoluenes, and methyl tolyl ethers in carbon disulphide (" AnalaR ") showed that of each of the three groups of compounds each isomer had a characteristic absorption band (see Table 3). The average molecular extinction coefficients were determined from the optical densities of a series of standard solutions. In a 1 mm. cell, solutions with concentrations 1—2 mg./ml. had optical densities suitable for analysis.

In the chlorotoluene mixture collected by vapour-phase chromatography of fraction (*b*) (above), the concentrations of the *ortho*- and *meta*-isomers were calculated by means of the Beer–Lambert law; the *para*-isomer concentration was deduced from a graph of the ratio of *ortho*- to *para*-chlorotoluene in a series of synthetic mixtures against the ratio of the optical densities of the mixtures at 13·41 and 12·45 mμ.

TABLE 3.

	λ (mμ)	Mol. extinction coeff.		λ (mμ)	Mol. extinction coeff.
o-Chlorotoluene	13·41	436 ± 3	*p*-Bromotoluene	12·51	344 ± 14
m-Chlorotoluene	12·98	263 ± 2	Methyl *o*-tolyl ether	13·38	370 ± 4
p-Chlorotoluene	12·45	372 ± 3	Methyl *m*-tolyl ether...	13·08	150 ± 6
o-Bromotoluene	13·45	412 ± 3	... Methyl *p*-tolyl ether ...	12·26	212 ± 9
m-Bromotoluene	13·02	241 ± 9			

TABLE 4. *Isomer ratios obtained by spectroscopic analysis.*

Expt.	Chlorotoluenes (%)			Bromotoluenes (%)			Methyl tolyl ethers (%)		
no.	*o*-	*m*-	*p*-	*o*-	*m*-	*p*-	*o*-	*m*-	*p*-
1	62·7	26·1	11·2	68·3	21·9	9·8	74·7	14·7	10·6
2	65·0	23·4	11·6	66·8	23·8	9·4	73·3	15·3	11·4
3	63·8	25·6	10·6						
Average	63·8	25·0	11·1	67·55	22·85	9·6	74·0	15·0	11·0

The relative concentrations of isomers in the bromotoluene and methyl tolyl ether mixtures were calculated by means of the Beer–Lambert law. For details see Table 4.

Synthetic mixtures were analysed before and after collection by vapour-phase chromatography. Results (Table 5) confirmed that the collection technique was quantitative within experimental error of the analytical procedure.

TABLE 5. *Isomer ratios of synthetic mixtures before and after vapour-phase chromatography.*

	Chlorotoluenes (%)			Bromotoluenes (%)			Methyl tolyl ethers (%)		
	o-	*m*-	*p*-	*o*-	*m*-	*p*-	*o*-	*m*-	*p*-
Before collection	62·5	22·0	15·5	67·0	21·9	11·1	74·7	14·8	10·5
After collection	63·0	22·5	14·5	69·5	19·2	11·3	75·7	13·5	10·8
Composition of synthetic mixture (by wt.)				67·9	21·7	10·4	74·6	15·2	10·2

Reaction of Methyl Radicals with Nitrobenzene.—Di-*tert.*-butyl peroxide (13 g.), purified nitrobenzene (90 ml.), and benzene (10 ml.) were refluxed together for 30 hr., the temperature being kept at about 143° as above. All material boiling below 120°/12 mm. was removed through a fractionating column; vapour-phase chromatography showed that this fraction contained no nitrotoluenes. The residue was examined by vapour-phase chromatography on a column (760 cm. × 8 mm.) packed with a mixture of 2 : 4 : 7-trinitrofluorenone (20 parts) and 30—50 mesh " Sil-o-cel " firebrick (97½ parts). The column was operated at 200° at slightly reduced pressure with a carrying stream of nitrogen (30 ml./min.). Injection of a sample of the residue into the column gave four peaks, one intense with retention time 40 min. and three smaller peaks with retention times 49½, 60½, and 72 min. These were shown to be due to nitrobenzene and *o*-, *m*-, and *p*-nitrotoluene respectively. The relation between peak area and quantity of material was determined for the nitrotoluenes by injecting standardised

mixtures of the isomers under the conditions of temperature, pressure, and flow-rate used for analysis of the product. Two determinations of the isomer ratios in the reaction product were then made, in two different sets of conditions:

Expt. no.	Column temp.	Flow rate (ml./min.)	Inlet pressure (mm.)	Outlet pressure (mm.)
1	190°	37	627	284
2	180°	33	575	250

The isomer ratios, expressed as percentages are:

	Nitrotoluenes		
Expt. no.	*o*-	*m*-	*p*-
1	64·3	6·4	29·2
2	66·5	5·8	27·7
Average	65·4	6·1	28·45

Reaction of Methyl Radicals with Benzonitrile.—Di-*tert.*-butyl peroxide (13 g.), purified benzonitrile (90 ml.), and benzene (10 ml.) were refluxed together for 48 hr., the temperature being kept at about 133° as above. After being heated with dilute hydrochloric acid for 3 min., 1 ml. of the mixture gave a negative test with 2 : 4-dinitrophenylhydrazine. All material boiling below 100° was removed, and the residue was fractionated, unchanged benzonitrile (containing no tolunitriles) distilling at 95°/17 mm. The residue was examined by vapour-phase chromatography in the column described above for the nitrobenzene experiments, operated at 190° at atmospheric pressure with a carrying stream of nitrogen (90 ml./min.). It gave an intense peak with retention time 34 min., a large peak with retention time 41 min., and two small peaks with retention times 53 and 57½ min. These were shown by comparison to be due to benzonitrile and *o*-, *m*-, and *p*-tolunitrile respectively. The peaks due to *m*- and *p*-tolunitrile were not completely resolved; and reduction of the column temperature to 183° gave no marked improvement. The quantity–area relations for the tolunitrile peaks were established as for nitrotoluene, and two determinations of the product composition were made with a column temperature of 183°, flow rate 90 ml./min., inlet pressure 1153 mm., and outlet pressure 756 mm. The isomer ratios found are expressed as percentages:

	Tolunitriles		
Expt. no.	*o*-	*m*-	*p*-
1	48·4	6·0	45·6
2	47·7	11·9	40·4
Average	48	9	43

Because of the unsatisfactory resolution of *m*- and *p*-tolunitrile, their relative concentrations could not be determined with accuracy and the figures given are approximate only.

Reaction of Methyl Radicals with a Mixture of Benzene and Chlorobenzene.—Di-*tert.*-butyl peroxide (13 g.), benzene (50 ml.), and chlorobenzene (50 ml.) were refluxed together for 160 hr., the temperature remaining at 93—97° and no acetone distilling. All material boiling below 100°/25 mm. was collected and examined by vapour-phase chromatography in the column packed with silicone rubber on firebrick described above, operated at 200°. The distillate gave large peaks corresponding to chlorobenzene and benzene, a very small peak due to chlorotoluenes, peaks due to low-boiling materials presumably formed by the decomposition of unchanged peroxide at the high temperature of the column, but no peak corresponding to toluene.

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357. *The Oxidation of Aromatic Hydrocarbons and Phenols by Trifluoroperoxyacetic Acid.*

By R. D. Chambers, P. Goggin, and W. K. R. Musgrave.

Benzene homologues other than toluene undergo electrophilic hydroxylation on treatment with trifluoroperoxyacetic acid. Further oxidation then occurs, to give quinones. An alkyl group in the *para*-position with respect to the hydroxyl group introduced migrates so that the *para*-quinone can be formed.

By starting with the phenols, good yields of some quinones have been obtained.

In practically all the known examples of the hydroxylation of aromatic hydrocarbons the reactions are ascribed to attack either by free radicals such as hydroxyl or benzoate radicals, or by addition of the so-called " double-bond reagents " followed by the elimination of water [1,2] to give the phenol. In some cases it is claimed that these double-bond reagents function simply as sources of hydroxyl radicals.[1] When the oxidation proceeds beyond the quinol stage without leaving a trace of earlier products as, for example, when dichromates are used as oxidising agents, free radicals are again postulated as intermediates.[3]

There are two cases where it is suggested that an electrophilic reaction has occurred. In one of these the hydroxyl cation was produced from hydrogen peroxide in acetic–sulphuric acid and used to prepare mesitol from mesitylene.[4] In the other, where peroxybenzoic acid was the oxidant,[5] there is little detail given and only polycyclic aromatic compounds were used. Peroxyacetic acid, which like peroxybenzoic acid is used to afford glycols from olefins and is also accepted for this purpose as an electrophilic reagent,[6] has been said to give no quinone from aromatic hydrocarbons [7] and, when it is used in a modified form simply as hydrogen peroxide and glacial acetic acid, reaction has occurred under such conditions that no decision on the mechanism has been possible. When peroxyacetic acid is used on phenols [8] the first step in the attack is at the *ortho*-position and, by analogy with the action of acyl peroxides on phenols, may occur by a bimolecular " four-centre " process.[9]

Since trifluoroperoxyacetic acid is a much better oxidising agent than any of the non-fluorinated peroxyacids,[10] and since Bourne *et al.*[11] have shown that the mixed anhydrides derived from trifluoroacetic acid are ionised slightly into negative trifluoroacetate ions and positive acylium ions, it seemed that if the other peroxyacids could be considered as electrophilic reagents then trifluoroperoxyacetic acid was likely to be an excellent source of positive hydroxyl ions. This was confirmed by treating certain benzene homologues with about $1\frac{1}{2}$ equivalents of trifluoroperoxyacetic acid at 0°. The peroxy-acid was prepared *in situ* by adding " high-test peroxide " to a solution of the hydrocarbon and trifluoroacetic anhydride in methylene chloride. Since the equilibrium in which trifluoroperoxyacetic acid is formed is set up instantaneously,[10] $(CF_3{\cdot}CO)_2O + H_2O_2 \rightleftharpoons CF_3{\cdot}CO_3H + CF_3{\cdot}CO_2H$, it was not necessary to form it before mixing with the hydrocarbon

[1] Waters, *Ann. Reports*, 1945, **42**, 130.
[2] Schoental, in Biochemical Symposium No. 5, 1949, p. 3 (Biological Oxidation of Aromatic Rings), ed. R. T. Williams; Cook and Schoental, *J.*, 1950, 47; Cross and Heiberg, *Ber.*, 1900, **33**, 2015; Perret and Perrot, *Helv. Chim. Acta*, 1945, **28**, 558; Milas, *J. Amer. Chem. Soc.*, 1937, **59**, 2342.
[3] Waters, *Trans. Faraday Soc.*, 1946, **42**, 184; Gee, *ibid.*, 197; Cason, " Organic Reactions," ed. R. Adams *et al.*, John Wiley, New York, 1948, Vol. IV, p. 305.
[4] Derbyshire and Waters, *Nature*, 1950, **165**, 401.
[5] Roitt and Waters, *J.*, 1949, 3060.
[6] Swern, " Organic Reactions," Ed. by R. Adams *et al.*, John Wiley, New York, 1953, Vol. VII, p. 378.
[7] Arnold and Larsen, *J. Org. Chem.*, 1940, **5**, 250.
[8] Boeseken and Metz, *Rec. Trav. chim.*, 1935, **54**, 345.
[9] Walling and Hodgdon, *J. Amer. Chem. Soc.*, 1958, **80**, 228.
[10] Emmons, *ibid.*, 1954, **76**, 3468, 3470; Emmons, Pagano, and Freeman, *ibid.*, p. 3472; Emmons and Pagano, *ibid.*, 1955, **77**, 89, 4557; Emmons and Lucas, *ibid.*, p. 2287.
[11] Bourne, Randles, Stacey, Tatlow, and Tedder, *ibid.*, 1954, **76**, 3206 and earlier papers.

solution. In later experiments it was found that trifluoroacetic acid could be used instead of the anhydride: the yields were lower by one-third but the same products were obtained and its use avoids the losses incurred in preparing the anhydride.

A 30—40% conversion of alkylbenzenes into a mixture of phenols and quinone was effected. This was separated after methylation, a process which caused the loss of most of the quinone, the yield of which had to be determined by eluting a separate portion of the original reaction mixture through an alumina column with methylene chloride or light petroleum. Except in the case of mesitylene, liquid chromatography could not be used to separate the whole mixture because the phenols are very strongly adsorbed on activated alumina and when deactivated alumina is used it is not a feasible method.[12]

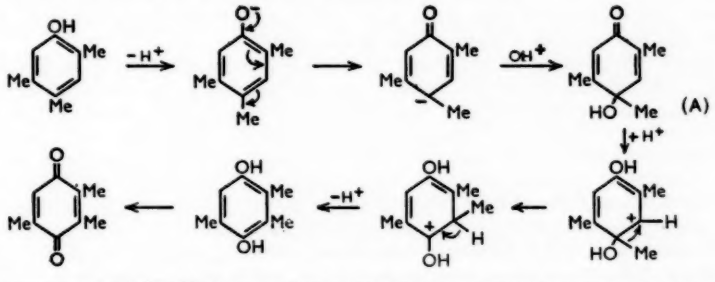
The aqueous layer from the reaction contained only trifluoroacetic acid and traces of a gum; no appreciable breakdown of the aromatic ring or tar formation appeared to have occurred.

The proof that electrophilic hydroxylation occurs came from the reactions with *m*-xylene and 1,2,4-trimethylbenzene. In the former the products were 2,6- and 2,4-xylenol and *m*-xyloquinone in yields of approximately 15%, 35%, and 20% respectively based on the amount of hydrocarbon used. They were identified mainly by gas–liquid chromatography after calibration of the column with authentic specimens of the methyl ethers and quinones. This method would not differentiate between methyl 2,4- and 3,5-xylyl ether but the infrared spectrum showed no trace of the latter. *m*-Xyloquinol was also isolated in the form of its dimethyl ether, but this is almost certainly all formed by methylation of the quinone and accounts for its disappearance.[13]

Oxidation of 1,2,4-trimethylbenzene gave 2,3,6- and 2,4,5-trimethylphenol, and the quinone. Again gas–liquid chromatography would not differentiate between methyl 2,4,5- and 2,3,5-trimethylphenyl ether, but the infrared spectrum showed that the 2,3,5-isomer was absent.

It has not yet been possible to confirm the mechanism by the hydroxylation of toluene because, under conditions necessary to initiate reaction, reaction is vigorous, giving a complex mixture which is not easy to separate. Benzene behaves similarly. In this connection the inability of Bourne *et al.*[11] to acylate benzene and toluene with mixed anhydrides is worth noting.

When mesitylene is oxidised it gives mesitol in good yield together with a small amount of 2,3,5-trimethylbenzoquinone. The latter probably results from the formation and rearrangement of mesityl "quinole"; this compound itself has not been isolated from the reaction mixture but by treating 2,4,5-trimethylphenol with trifluoroperoxyacetic acid the corresponding 2,4,5-trimethyl" quinole " (A) has been isolated in about 10% yield. The mechanism for the complete process is probably as annexed.



Bamberger and Rising[14] claim to have isolated very small amounts of this and other "quinoles" by the oxidation of benzene homologues with Caro's acid. They rearranged

[12] Schneider and Oberkobusch, *Brennstoff-Chem.*, 1951, **32**, 110.
[13] Rao, Rao, and Seshadri, *Proc. Indian Acad. Sci.*, 1948, **27**, *A*, 245.
[14] Bamberger and Rising, *Ber.*, 1900, **33**, 3636; 1903, **36**, 2028.

them in the presence of either acid or alkali but this has not previously been confirmed because other workers [15] have been unable to repeat their preparation of the "quinoles." Attempts to prepare other "quinoles" by means of trifluoroperoxyacetic acid are now being made.

Since fairly high yields of quinones were obtained, even under unsuitable conditions, in the cases where their formation was possible without rearrangement, we compared this use of peroxytrifluoroacetic acid with other methods of preparing quinones. Certain phenols (*o*- and *m*-cresol, 2,3-dimethylphenol) gave only resins, while others gave 50—80% yields of quinone. In these reactions the temperature was allowed to rise after addition of the peroxide, and the colour changed through red to black (presumably formation of semiquinones), then to orange-yellow during about 8 hours, whereafter the quinone was obtained almost pure. The method generally gives a better yield than does chromic acid, it is easier to isolate and purify the product, and in some cases, *e.g.*, 2,3,5-trimethylphenol, chromic acid will not effect direct oxidation and either Fremy's salt [16] or the route through the azo-dye [17] has to be used.

Experimental

m-*Xylene.*—(*a*) To trifluoroacetic anhydride (30 g.) and *m*-xylene (16 g.), dissolved in methylene chloride (50 ml.) and cooled to 0°, 85% hydrogen peroxide (6 ml.) was added with stirring during 30 min. Stirring was continued at 0° for 24 hr., the colour changing through dark red to yellow. The mixture was then neutralised with solid sodium hydrogen carbonate after addition of a few ml. of water. After separation, the aqueous layer was extracted with methylene chloride (3 × 10 ml.) and the extracts were added to the rest of the organic layer.

The aqueous layer was then acidified with dilute sulphuric acid and extracted continuously with methylene chloride. Drying and distillation of the methylene chloride and the trifluoroacetic acid left only a minute amount of a gum. The methylene chloride solutions were dried ($MgSO_4$) and distilled, to give (i) methylene chloride, (ii) *m*-xylene (10 g.), b. p. <90°/20 mm., and (iii) a red oily residue (5·6 g.).

A sample of this red oil (1·0 g.) was eluted through a column of activated alumina with methylene chloride, to give *m*-xyloquinone (0·25 g.), m. p. 71°, mixed m. p. 72°. The phenolic constituents remained on the column and could not be removed quantitatively even on continuous extraction with methyl alcohol.

Methylation of the red oil (3 g.) in methanol (6 ml.) with dimethyl sulphate (3 g.) and a 30% aqueous solution of sodium hydroxide (7 g.) first at −5° and then under reflux gave, after ether-extraction, a dark liquid (2·5 g.) which was examined by gas–liquid chromatography in a column (length 232 cm., internal diameter 6 mm.) packed with 12 g. of a mixture of "Apiezon L" (4 pt.) and "Celite 545" (10 pt.). With the column at 194°, a nitrogen flow-rate of 38 ml./min., inlet pressure being atmospheric and a vacuum of −22 cm. being applied at the outlet, the mixture separated into three main components with peak-maximum times of 6½ min., 8 min., and 17½ min. respectively. Comparison of these chromatograms with those of authentic specimens and with those of mixtures of the product and authentic specimens showed that the components were methyl 2,6-xylyl ether, either the 2,4- or the 3,5-xylyl ether or a mixture of the two, and *m*-xyloquinol dimethyl ether respectively.

The methyl ethers were condensed out of the nitrogen stream after passing through the column, and infrared analysis of the second component showed that it consisted mainly of the 2,4-isomer, $\nu_{max.}$ (no solvent) 1040, 877, 804, 754, 710 cm.$^{-1}$ (authentic specimen 1039, 877, 804, 754, 710), together with a little 2,6-isomer, $\nu_{max.}$ (no solvent) 1094, 1068, 1018, and 771 cm.$^{-1}$ (authentic specimen 1093, 1064, 1015, 768), due to overlapping with the first peak, but that the 3,5-isomer was absent (no band at or near 952 or 691 cm.$^{-1}$ as for an authentic specimen).

From the yields of methyl ethers (85%) obtained by methylation of the authentic phenols, the areas of the peaks obtained by chromatography, and the amount of quinone isolated by liquid chromatography, it was calculated that the red oil (5·6 g.) from *m*-xylene (6 g.) contained 2,6-xylenol 1 g., 2,4-xylenol 2·5 g., *m*-xyloquinol 0·7 g., and *m*-xyloquinone 1·4 g.

(*b*) Repetition of the experiment with *m*-xylene (12·9 g.), trifluoroacetic acid (20 g.), methylene chloride (50 ml.), and 85% hydrogen peroxide (5·3 ml.) gave recovered *m*-xylene

[15] Cosgrove and Waters, *J.*, 1951, 388.
[16] Teuber and Rau, *Chem. Ber.*, 1953, **86**, 1036.
[17] Smith, Opie, Wawzonek, and Prichard, *J. Org. Chem.*, 1939, **4**, 318.

(9·3 g.) and a red oil (3·3 g.) which contained 2,6- (0·75 g.) and 2,4-xylenol (0·75 g.), *m*-xyloquinol (0·7 g.), and *m*-xyloquinone (0·8 g.).

1,2,4-*Trimethylbenzene*.—Trifluoroacetic anhydride (33 g.), 1,2,4-trimethylbenzene (19 g.), and 85% hydrogen peroxide (6·5 ml.) in methylene chloride (50 ml.) gave recovered hydrocarbon (12 g.) and a red oil (6·2 g.) which contained 2,5,6- (1 g.) and 2,4,5-trimethylphenol (1·3 g.) and the quinone (1·7 g.) (*monosemicarbazone*, m. p. and mixed m. p. 252°; Found: C, 57·6; H, 6·3. $C_{10}H_{13}O_2N_3$ requires C, 58·0; H, 6·3%). A fourth component was probably the quinol; its dimethyl ether was eluted so slowly from the gas–liquid chromatography column that it was not collected.

The methyl ethers of 2,5,6- and 2,4,5-trimethylphenol had peak maximum times of 6 min. 50 sec. and 8 min. 50 sec. respectively when eluted through the gas–liquid chromatography column at 202° (nitrogen flow rate 38 ml./min.; inlet pressure atmospheric; outlet vacuum −13·5 cm.).

Methyl 2,4,5-trimethylphenyl ether, $\nu_{max.}$ (no solvent) 1271, 1214, 1100, 873, 841 cm.$^{-1}$ (authentic, 1275, 1215, 1099, 877, 845 cm.$^{-1}$), was differentiated from the 2,3,5-trimethyl isomer [authentic, $\nu_{max.}$ (no solvent) 1189, 1151, 1117, 964, 832 cm.$^{-1}$] by comparing its infrared spectrum with those of authentic specimens. There was no 2,3,5-trimethyl isomer in the reaction mixture.

Mesitylene.—Trifluoroacetic acid (19 g.), mesitylene (18·7 g.), and 85% hydrogen peroxide (6 ml.) in methylene chloride (50 ml.) gave recovered mesitylene (14 g.) and a red oil (4·5 g.) which on elution through an alumina column with methylene chloride gave the quinone (0·75 g.) (monosemicarbazone, m. p. and mixed m. p. 252°) and crude mesitol (3·5 g.) which, purified by sublimation, had m. p. 70° and mixed m. p. 70°.

Preparation of 2,4,5-*Trimethyl" quinole "*.—2,4,5-Trimethylphenol (9·7 g., 0·07 mol.) and trifluoroacetic acid (10 g., 0·07 mol.) in methylene chloride (50 ml.) were treated with 85% hydrogen peroxide (8·2 ml., 0·28 mol.) at room temperature with stirring. After 24 hr. the mixture was neutralised with sodium hydrogen carbonate. The aqueous layer was separated and extracted with methylene chloride. The united extracts, when dried ($MgSO_4$) and evaporated, left a red oil (6·7 g.) which was eluted through an alumina column (36 cm. × 2 cm.) with methylene chloride until the first coloured fraction was completely removed. Evaporation gave a yellow-brown oil (2·67 g.), which was treated with a few ml. of ether and left exposed to the air. White crystals of " 2,4,5-trimethylquinole " [14] (1·04 g.; m. p. 113°) separated. After recrystallising from water and subliming it had m. p. 116° (Found C, 71·1; H, 8·4. Calc. for $C_9H_{12}O_2$: C, 71·0; H, 7·9%) and formed a *benzoate*, m. p. 93° (from alcohol and water) (Found: C, 75·2; H, 6·5. $C_{16}H_{16}O_3$ requires C, 75·0; H, 6·3%). The infrared spectrum of the quinole showed $\nu_{max.}$ (KBr discs) 3522 (OH) 1650 cm.$^{-1}$ (C=O) and no benzene absorption (1610—1450, 3500—3000 cm.$^{-1}$).

Oxidation of Phenols to Quinones.—(a) 2,6-*Xylenol*. To 2,6-xylenol (10 g.) and trifluoroacetic acid (10 g.) in methylene chloride (50 ml.) at room temperature were added, all at once, 10 ml. of 85% hydrogen peroxide. The mixture was stirred and within 30 min. the heat of reaction caused the methylene chloride to reflux. During the next 7 hr. the temperature gradually fell and the colour changed through red to black and then orange-yellow. The last stage was completed by refluxing the mixture for 30 min. After neutralisation with aqueous sodium hydrogen carbonate and extraction of the aqueous layer with methylene chloride, the combined methylene chloride fractions were dried ($MgSO_4$) and evaporated, to give almost pure *m*-xyloquinone (8·6 g., 77%), m. p. 69°. Recrystallisation from ethanol or ether gave a specimen with m. p. 71° (mixed m. p. 72° with an authentic specimen [17] of m. p. 74·5°) (lit., 73°).

(b) 3,5-*Xylenol*. The phenol (8·2 g.) gave crude *m*-xyloquinone (5·3 g., 57%) which was purified by elution, with methylene chloride, through alumina to give pure *m*-xyloquinone (5·2 g.), m. p. and mixed m. p. 74°.

(c) p-*Xylenol*. The phenol (8·4 g.) gave crude *p*-xyloquinone (4·8 g., 50%), m. p. 120°. Recrystallised from ethanol it had m. p. and mixed m. p. 124°.

(d) 2,3,5-*Trimethylphenol*. This phenol (10 g.) gave a crude quinone (7 g.) (monosemicarbazone, m. p. 252° and mixed m. p. 252°).

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358. *The Cumulative Effect of Substituents on the Reaction of NN-Dimethylanilines with Allyl Bromide.*

By H. P. Crocker and Brynmor Jones.

The formation of quaternary salts from allyl bromide and substituted dimethylanilines in aqueous acetone has been studied. With mono-substituted amines, *meta*- and *para*-substituents alter the reaction velocity solely by their effects on the activation energy. For all the 3 : 5-disubstituted amines examined, the rates are in close agreement with those calculated, the effects of the two groups being assumed to be additive. In other cases, a strict additivity of group effects is not observed, and with certain *NN*-dimethyl-*o*- and -*p*-anisidine derivatives the observed rate is almost double that calculated, with the activation energy and frequency factor both lower than would be expected.

For some reactions of benzene derivatives for which the frequency factor is essentially constant it has been shown that the cumulative effect on the reaction velocity of two nuclear substituents is often additive.[1] In an effort to assess the generality of this principle, the formation of quaternary ammonium salts from disubstituted *NN*-dimethylanilines and allyl bromide has been studied kinetically.

In two previous investigations it was shown that *meta*- and *para*-substituents affect the rate of reaction of *NN*-dimethylaniline with methyl iodide by contributions to the activation energy only. In the first of these, Laidler [2] used nitrobenzene as solvent, but this suffered from the drawback that equilibration occurred. In the second, Evans, Watson, and Williams [3] used methanol (a solvent used in other investigations by later workers [4]) but close examination showed that at 45°, in 0·1M-solution, a slow reaction leading to the formation of iodide ions occurred between methyl iodide and the solvent. This methanolysis, which tended to equilibrium, was sufficient to lead to inaccuracies in rate measurements, particularly with the less reactive bases. Fortunately, Davies and Cox [5] had shown that the reaction between certain *NN*-dimethylanilines and allyl bromide could be followed kinetically in 10% aqueous acetone without complications from the concurrent hydrolysis of the halide, and their results indicated that the tendency towards equilibrium could be avoided by increasing the proportion of water in the solvent. Accordingly, allyl bromide was adopted as halide in preference to methyl iodide, and with 25% aqueous acetone as solvent, rates of the reaction with a wide range of bases could be followed conveniently and be reproduced accurately over the temperature range 0—35°. With an initial concentration of amine twice that of the halide, no tendency towards equilibrium was noted over the range (15—65% completion) of the reaction normally followed, and, in general, the hydrolysis of the halide (k_{20} $1{\cdot}71 \times 10^{-7}$; k_{35} $8{\cdot}52 \times 10^{-7}$ sec.$^{-1}$) could be ignored. However, because of this complication the extremely slow reaction with *NN*-dimethyl-1-naphthylamine could not be determined, and the rates recorded for the very unreactive *m*-nitro- and 3-chloro-2-methoxy-*NN*-dimethylaniline are slightly in error. In view of the operation of several possible factors, no corrections were attempted. As could be expected from the work of Holtzschmidt and Potapoff,[6] a distinct autocatalysis was noted: velocity coefficients calculated in the usual way increased by about 5% during

[1] (*a*) Bradfield and Brynmor Jones, *J.*, 1928, 1006; Brynmor Jones, *J.*, 1935, 1831; 1942, 418, 676; Sleight and Brynmor Jones, *J.*, 1954, 1775; (*b*) Stubbs and Hinshelwood, *J.*, 1949, S71; (*c*) Branch and Brynmor Jones, *J.*, 1954, 2317; 1955, 2921; (*d*) Brynmor Jones and Robinson, *J.*, 1955, 3845; (*e*) Brynmor Jones and Watkinson, *J.*, 1958, 4064.

[2] Laidler, *J.*, 1938, 1786.

[3] Evans, Watson, and Williams, *J.*, 1939, 1345.

[4] (*a*) Brown and Fried, *J. Amer. Chem. Soc.*, 1943, **65**, 1841; (*b*) Evans, *J.*, 1944, 422; (*c*) Weale, *J.*, 1954, 2959.

[5] Davies and Cox, *J.*, 1937, 614.

[6] Holtzschmidt and Potapoff, *Acta Physicochim. U.R.S.S.*, 1937, **7**, 778; Potapoff and Holtzschmidt, *J. Phys. Chem., U.S.S.R.*, 1941, **15**, 1094.

the reaction, and velocity coefficients were therefore obtained by extrapolation to zero time, the plot being linear within the error of experiment.

The kinetic data obtained are shown in Table 1. The solvent throughout was 25% v/v aqueous acetone, and the initial concentrations at 20° of the allyl bromide and dimethylaniline were 0·1M and 0·2M, respectively. The velocity coefficients recorded are believed be accurate to within 1·5%, and could be duplicated within these limits.

TABLE 1. *Reaction of allyl bromide and substituted* NN-*dimethylanilines: velocity coefficients and activation energies.*

Substituent	10^4k (l. mole^{-1} sec.$^{-1}$)				E (cal.)	$\log_{10} PZ$
	0·0°	19·75°	24·9°	35·0°		
p-OEt	7·00	28·3	—	—	11,230	5·85
p-OMe	6·92	28·0	—	—	11,260	5·85
p-Me	3·06	13·2	18·4	35·4	11,710	5·86
m-Me	1·52	6·68	9·60	18·9	12,060	5·83
H	1·18	5·34	7·80	15·0	12,130	5·78
p-F	—	5·24	—	—	—	—
(*NN*-Dimethyl-2-naphthylamine)	0·770	3·63	—	10·4	12,410	5·82
m-OMe	0·845	3·90	5·53	11·1	12,350	5·80
p-Cl	0·315	1·56	2·29	4·66	12,880	5·81
p-Br	0·260	1·29	1·87	3·89	12,980	5·79
p-I	—	1·25	—	—	—	—
m-F	—	0·726	—	2·28	13,470	5·91
m-Cl	—	0·604	—	1·86	13,310	5·73
m-Br	—	0·580	—	1·84	13,540	5·85
m-NO_2	—	0·134	—	—	—	—
(*NN*-Dimethyl-1-naphthylamine)	—	*ca.* 0·02	—	—	—	—
o-OMe	1·96	9·26	13·6	27·0	12,540	6·33
3-Br, 5-Me	—	0·744	—	—	—	—
3-Br, 4-Me	—	1·65	—	—	—	—
4-Br, 3-Me	—	1·82	—	5·40	12,800	5·83
3-Br, 5-OMe	—	0·418	—	—	—	—
3-Cl, 5-Me	—	0·776	—	—	—	—
3-Cl, 4-Me	0·368	1·79	—	5·20	12,650	5·69
4-Cl, 3-Me	—	2·23	—	—	—	—
3-Cl, 5-OMe	—	0·438	—	1·385	13,550	5·74
4-Cl, 3-OMe	—	1·48	—	—	—	—
3-Me, 5-Me	1·92	8·30	—	23·45	11,960	5·85
3-Me, 4-Me	—	16·4	—	—	—	—
3-OMe, 4-OMe	5·94	—	—	—	—	—
3-Me, 5-OMe	—	4·92	—	—	—	—
4-Me, 3-NO_2	—	0·360	—	—	—	—
3-Br, 4-OMe	—	5·90	—	16·05	11,770	5·55
3-Cl, 4-OMe	1·40	5·95	—	16·0	11,650	5·47
3-F, 4-OMe	1·44	5·99	—	—	11,500	5·35
3-I, 4-OMe	—	7·04	—	18·8	11,560	5·48
4-OMe, 3-NO_2	—	1·53	—	4·41	12,460	5·48
4-Cl, 2-OMe	0·706	3·55	—	10·65	12,970	6·23
5-Cl, 2-OMe	—	1·99	—	6·02	13,060	6·04
2-OMe, 5-OMe	1·43	7·00	—	—	12,790	6·39
5-F, 2-OMe	0·510	2·47	—	7·32	12,740	5·90
5-I, 2-OMe	—	2·01	—	6·20	13,260	6·19
5-Me, 2-OMe	2·22	10·9	—	—	12,810	6·59
2-OMe, 5-NO_2	—	0·536	—	1·76	13,990	6·17
3-Cl, 2-OMe	—	0·101	—	—	—	—

Monosubstituted Bases.—Although the non-exponential factor was sensibly constant for the reaction of wide range of *meta*- and *para*-substituted bases with methyl iodide,[2,3] Evans[4b] considered that significant variations in P occurred with alkyl substituted *NN*-dimethylanilines of similar reactivity. Furthermore, for the reaction of allyl bromide with *p*-chloro- and *p*-bromo-*NN*-dimethylaniline in 10% aqueous acetone, remarkably concordant results showing a wide divergence in the non-exponential term had been obtained by two independent groups of workers (see Table 2).

At the outset, therefore, it was thought necessary to check the variation of E and P with 25% aqueous acetone as solvent. For six *meta*- and *para*-substituted bases (including the

p-chloro- and *p*-bromo-derivatives) rate measurements were carried out at four temperatures. No significant variations in *P* were observed.

The general order of reactivities for the series of amines is in harmony with previous work and the Hammett equation is obeyed.

NN-Dimethyl-2-naphthylamine gave a slightly lower rate than *NN*-dimethylaniline, the ratio of rates, 0·68, being similar to the ratio of reactivites of 2-naphthylamine and

TABLE 2.

	Davies and Cox [5]		Vorob'ev [7]	
Amine	*E* (cal.)	$\log_{10} PZ$	*E* (cal.)	$\log_{10} PZ$
p-Chloro-*NN*-dimethylaniline	12,250	5·41	12,250	5·40
p-Bromo-*NN*-dimethylaniline	13,250	4·70	13,260	4·69

aniline towards benzoyl chloride.[1b] Whereas in the benzoylation 1-naphthylamine was one-fifth as reactive as the 2-isomer, *NN*-dimethyl-1-naphthylamine proved to be so unreactive that the rate could not be determined, probably owing to steric retardation of the reaction by the adjacent *peri*-hydrogen atom.[8]

Cumulative Effect of Substituents.—In recent investigations,[1b,d] the cumulative effect of nuclear substituents on the reaction at a benzene side-chain has been assessed in terms of the free energy of activation, which reflects changes in the activation energy if the entropy of activation remains constant. Since in the present study the non-exponential term is not always constant, the results are analysed in terms of the velocity coefficients.

For the disubstituted base $C_6H_3XY{\cdot}NMe_2$, if the contributions to the activation energy of the groups X and Y are additive, then

$$k_{XY} = A_{XY}(k_X/A_X)(k_Y/A_Y)(A_U/k_U)$$

which reduces to $k_{XY} = k_X k_Y/k_U$ on the assumptions that (i) $A_{XY} = A_X$, and (ii) $A_U = A_Y$. This might be expected to apply when X is an *ortho*-substituent (and where $A_X \neq A_U$). When rates calculated according to this equation are compared with the observed values, three distinct groups of results are observed (see Table 3). Within the limits of experi-

TABLE 3. *Disubstituted bases: comparison of observed and calculated rates.*

	10^4k_{20}				10^4k_{20}		
Substituents	Obs.	Calc.	$100k_{obs.}/k_{calc.}$	Substituents	Obs.	Calc.	$100k_{obs.}/k_{calc.}$
3-Br, 5-Me	0·74	0·726	103	3-Br, 4-OMe ...	5·90	3·04	194
3-Br, 5-OMe ...	0·418	0·424	99	3-Cl, 4-OMe ...	5·95	3·17	188
3-Cl, 5-Me	0·776	0·756	104	3-F, 4-OMe ...	5·99	3·81	157
3-Cl, 5-OMe ...	0·438	0·441	99	3-I, 4-OMe	7·04	3·42	206
3-Me, 5-Me	8·30	8·36	99	3-NO_2, 4-OMe	1·53	0·703	218
3-Me, 5-OMe ...	4·92	4·88	101	5-Cl, 2-OMe ...	1·99	1·05	190
3-Me, 4-Me	16·4	16·5	99	5-F, 2-OMe ...	2·47	1·26	196
3-Br, 4-Me	1·65	1·43	115	5-I, 2-OMe	2·01	1·13	178
4-Br, 3-Me	1·82	1·61	113	5-Me, 2-OMe ...	10·9	11·6	94
3-Cl, 4-Me	1·79	1·49	119	2-OMe, 5-OMe	7·00	6·76	104
4-Cl, 3-Me	2·23	1·97	114	3-Cl, 2-OMe ...	0·101	1·05	9·6
4-Cl, 3-OMe ...	1·48	1·14	130	4-Cl, 2-OMe ...	3·55	2·70	131
4-Me, 3-NO_2 ...	0·360	0·331	109				
3-OMe, 4-OMe (at 0°)	5·94	4·96	120				

mental error (estimated at ±5%), the velocity ratios obtained for all the 3 : 5-disubstituted amines and for 3 : 4-dimethyl-*NN*-dimethylaniline show a strict additivity of group effects. This result is in full accord with earlier work on the hydrolysis of benzoic esters,[1c] with dipole-moment data,[9] and with values of the dissociation constants of disubstituted benzoic acids.[10]

[7] Vorob'ev, *J. Phys. Chem., U.S.S.R.*, 1940, **14**, 686.
[8] Cf. Price, Mertz, and Wilson, *J. Amer. Chem. Soc.*, 1954, **76**, 5131.
[9] Syrkin and Dyatkina, "Structure of Molecules," Butterworths, London, 1950, p. 225.
[10] Shorter and Stubbs, *J.*, 1949, 1180; Dippy, Hughes, and Laxton, *J.*, 1956, 2995.

For the toluidine derivatives and for 3 : 4-dimethoxy- and 4-chloro-3-methoxy-*NN*-dimethyl-aniline, the observed rates are all some 10—30% higher than the predicted values. This could arise from a slight increase in the non-exponential factor (A_{XY}) for the disubstituted base—an increase too small to be detected by experiment. However, a more likely explanation is that group interaction occurs, leading to greater electron-release by the substituents in the 3 : 4-positions, similar perhaps to the slight, but significant, lack of additivity of group dipole moments noted for *ortho*-substituted toluenes.[9] For the above compounds, any reduction of the extent of conjugation of the *para*-substituent with the aromatic ring would reduce the reaction rate, and appreciable steric inhibition of mesomerism by the substituent in the 3-position is clearly absent.

In the case of the five 3-halogeno- or 3-nitro-*NN*-dimethyl-*p*-anisidines examined the additivity principle is seriously violated and a well-defined group-interaction is manifest. Here there can be no question of additivity being masked by variations in A_{XY}—in fact for these compounds the mean experimental value for $\log_{10}PZ$ (5·47) is significantly lower than the value (5·80) found for the monosubstituted bases. In Table 4 these results are compared with those obtained from the hydrolysis of similarly substituted benzoic esters.

TABLE 4. *Velocity ratios of substituted* NN-*dimethyl*-p-*anisidines and ethyl* p-*anisates.*

Substituent	Alkaline hydrolysis (at 25°) $100\,k_{calc.}/k_{obs.}$	Menschutkin (at 20°) $100\,k_{obs.}/k_{calc.}$
3-Bromo-	148	194
3-Chloro-	143	188
3-Nitro-	143	218

(Velocity ratios for the ester hydrolysis have been inverted since this reaction is aided by electron-withdrawal from the reaction centre.) A similar type of interaction leading to an increase in electron density at the reaction centre is present for both series of compounds, but with the esters the effect seems to be far less marked.

This interaction seems to be polar rather than steric in origin. Any steric inhibition of the mesomeric effect of the *p*-methoxy-group by the adjacent halogen would lower the reaction rate. In fact, the velocity ratios increase as the size of the halogen is increased.

With *ortho*- and *para*-disubstituted benzene derivatives the dipole moments due to the individual groups are often not vectorially additive, and there is a close parallelism between the velocity ratios found for 3-substituted *p*-anisidines and the interaction moments of *p*-substituted anisoles given by Leonard and Sutton[11] (Table 5). Since, however, the

TABLE 5. *Comparison of the interaction moments of* p-*substituted anisoles and velocity ratios of* 3-*substituted* NN-*dimethyl*-p-*anisidines.*

Substituent	μ (int.)	$100k_{obs.}/k_{calc.}$
Fluoro	−0·06	157
Chloro	0·04	188
Bromo	0·15	194
Iodo	0·16	206
Nitro	0·37	218

magnitude of this effect is less with the benzoic esters than in the present case, the dimethylamino-group also seems to be involved in the interaction, and in this context the relatively slight departure from additivity found for 4-chloro-3-methoxy-*NN*-dimethylaniline may have significance.

The velocity ratios found for the 5-substituted *NN*-dimethyl-*o*-anisidines are very similar to those for the 3-substituted *p*-anisidine derivatives, minor differences perhaps being due to incursion of the *ortho*-effect. Again, large departures from additivity are accompanied by an observed value of $\log_{10}PZ$ appreciably lower than the expected value (that of *NN*-dimethyl-*o*-anisidine), and with the halogeno- and nitro-substituted compounds a similar type of group interaction is indicated. The close correlation between the

[11] Leonard and Sutton, *J. Amer. Chem. Soc.*, 1948, **70**, 1564.

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predicted and the observed rates for 2 : 5-dimethoxy-*NN*-dimethylaniline is comparable with the relatively normal velocity ratio found for the 3 : 4-dimethoxy-compound. Since methoxyl and halogen substituents have similar electronic effects, both results contrast strongly with the abnormal ratios associated with the similarly substituted halogeno-anisidines.

In their study of the benzoylation of disubstituted anilines, Stubbs and Hinshelwood [1b] included five compounds with the same substituents in similar orientation to those used in the present study, and the results are summarised in Table 6. Whereas the toluidine derivatives have given similar results for both reactions, there is no correlation between the ratios obtained for the *o*-anisidine derivatives. It is unfortunate that no 3-halogeno-4-methoxyanilines were studied, for a comparison of results for this series would be free from the complication that no *ortho*-effect is found for the benzoylation reaction.

TABLE 6. *Velocity ratios for disubstituted anilines and dimethylanilines.*

	$100k_{obs.}/k_{calc.}$			$100k_{obs.}/k_{calc.}$	
Substituents	Benzoylation (at 25°)	Menschutkin (at 20°)	Substituents	Benzoylation (at 25°)	Menschutkin (at 20°)
3-Me, 4-Me	95	99	5-Cl, 2-OMe	89	190
3-Me, 5-Me	92	99	5-NO_2, 2-OMe ...	65	231
3-Cl, 4-Me	113	119			

Finally, the very low rate given by 3-chloro-2-methoxy-*NN*-dimethylaniline exemplifies group interaction of a different character from that found for the preceding compounds. It is well known that the extent of conjugation of a methoxy-group with the benzene ring is much reduced by the presence of two flanking substituents,[12] and with this particular compound it seems that the inductive effect of the methoxy-group is virtually unopposed by the usual mesomeric effect. The steric requirements of the methoxy-group may here also be effectively increased.

EXPERIMENTAL

Kinetic Measurements.—For the reaction with methyl iodide the method of Evans, Watson, and Williams [3] was adopted with minor modifications. 2 c.c. portions of 0·2M-methyl-alcoholic solutions of methyl iodide and *NN*-dimethylaniline, freshly prepared at 45°, were mixed in black-painted, drawn-out test-tubes, which were then sealed and replaced in the thermostat. At intervals, tubes were withdrawn, and the contents analysed for iodide ions. Rate constants obtained, expressed in l. mole^{-1} sec.$^{-1}$, were as follows:

Substituent	H	*m*-Me	*p*-Me	*m*-OMe	*p*-OMe	*m*-Cl	*p*-Cl	*m*-Br	*p*-Br
10^4k (45·0°)	2·71	3·85	6·23	2·15	11·4	0·350	0·774	0·335	0·643

Generally, k was sensibly constant throughout the run, but with *p*-bromo-*NN*-dimethylaniline an asymptotic increase with time was noted which was unaltered when both reactants and the solvent were further purified in turn. The extent of solvolysis of 0·1M-solutions of methyl iodide was then found to be appreciable at 45°; 50 or 100 c.c. of solution were taken for each measurement:

Time (hr.)	0·0	6	12	17·5	24	42	72	120
$10^6[I^-]$ (mole/l.)	0	490	943	1345	1640	2650	3420	3810
10^7k_1	—	2·26	2·19	2·15	2·03	1·78	1·34	0·92

For the reaction of allyl bromide with dimethylanilines, 0·3M-solutions were prepared in aqueous acetone at 20°. 10 c.c. of the halide solution and 20 c.c. of the amine solution were introduced into separate arms of an H-shaped reaction vessel [1c] and the solutions were mixed when temperature equilibrium had been attained. At intervals, 2 c.c. samples were removed and added to light petroleum (b. p. 100—120°; 30 c.c.), and the solution was extracted thrice with 10 c.c. portions of distilled water. The combined aqueous extracts were acidified with 5 c.c. of 6N-nitric acid, 5·0 c.c. of 0·04N-silver nitrate solution were added, and the excess of silver nitrate was estimated by titration with 0·01N-ammonium thiocyanate by Volhard's method. The allyl bromide present in the aqueous solution did not affect the estimation.

[12] Everard and Sutton, *J.*, 1951, 16; Anzillotti and Curran, *J. Amer. Chem. Soc.*, 1943, **65**, 607.

The initial concentrations of the reactants at temperatures other than 20° were calculated from the corresponding density of the solvent:

Temperature	0·0°	19·75°	24·9°	35·0°
Density of solvent (g./c.c.)	0·8966	0·8767	0·8719	0·8617
Initial concentration of halide	0·1023	0·1000	0·09445	0·09830
Initial concentration of base	0·2046	0·2000	0·1989	0·1966

Velocity coefficients calculated from the usual expression $k_2 = [1/t(a - b)] \ln [a(b - x)/b(a - x)]$ increased linearly with time over the range of experiment (15—65% completion), and the observed values were extrapolated to zero time. Typical results are given below:

Reaction of p-*bromo*-NN-*dimethylaniline with allyl bromide in* 25% *v/v aqueous acetone at* 35·0°.

$10t$ (sec.)	269	360	454	634	828	1050	1320	1441	1620
10^5x	1770	2287	2760	3579	4334	5055	5785	6094	6487
10^4k (l. mole^{-1} sec.$^{-1}$)	3·95	4·00	4·00	4·04	4·09	4·11	4·17	4·21	4·25

k (extrapolated) $= 3{\cdot}89 \times 10^{-4}$.

With the exceptions noted below, the precision of the experimental method was satisfactory and results were readily reproducible. In every case the reaction mixture remained homogeneous. On account of its low solubility in aqueous acetone, the initial concentration of *p*-iodo-*NN*-dimethylaniline was 0·1M. The reaction with 3 : 4-dimethoxy-*NN*-dimethylaniline could not be followed at 20° because the end-point of the titration was obscured by an orange colour which developed when the ferric indicator was added.

Solvolysis of the Allyl Bromide.—The extent of hydrolysis of allyl bromide by the reaction medium at 20° and at 35° was determined by periodically analysing aliquot parts (10 or 5 c.c.) of a 0·2M-solution. First-order rate constants, as determined over the early stages of the reaction, were $1{\cdot}71 \times 10^{-7}$ sec.$^{-1}$ at 19·75° and $8{\cdot}52 \times 10^{-7}$ at 35·0°. This solvolysis was normally unimportant, except for the very unreactive bases such as 3-chloro-2-methoxy-*NN*-dimethylaniline.

With *NN*-dimethyl-1-naphthylamine, after 7 days at 20°, the reaction mixture had a bromide-ion concentration of 0·025 mole/l., corresponding to a rate constant of $2{\cdot}5 \times 10^{-6}$, but the solution had become very dark and solvolysis of the halide would have given a bromide-ion concentration of 0·01 mole/l.

Preparation of Solvents.—Methyl alcohol was purified according to Evans, Watson, and Williams.[3]

Acetone (3 vol.), purified by the method of Conant and Kirner,[13] was diluted with distilled water (1 vol.). The resultant mixture had n_D^{20} 1·3657, corresponding to 29·8% w/w of water. The same batch was used throughout the investigation.

Purification of Alkyl Halides.—Methyl iodide, purified by the method of Evans, Watson, and Williams,[3] had b. p. 42·6°/759 mm., n_D^{20} 1·5300.

Allyl bromide was dried over calcium chloride and twice fractionally distilled, material of b. p. 70·3°/769 mm., n_D^{20} 1·4692, being used for rate-measurements.

Substituted NN-*Dimethylanilines.*—All tertiary bases were treated to remove any primary or secondary amine present. The amine was refluxed with acetic anhydride (4 vol.), weak bases being heated for longer (3 hr.) than more strongly basic ones (½ hr.). The residue left after distillation of the greater part of the anhydride was taken up in ice-cold, dilute hydrochloric acid, and non-basic materials were extracted with ether. The tertiary base was liberated with ammonia, filtered off or extracted with ether, dried, and distilled under reduced pressure. Solids were crystallised several times from alcohol or aqueous alcohol. Liquid bases were further purified by way of the picrates, which were prepared in benzene solution and crystallised to constant m. p. from alcohol or acetic acid. The amine was recovered by decomposing the picrate with warm 10% sodium hydroxide solution, followed by ether-extraction. The ethereal solution was washed with water, dried, and distilled, finally under reduced pressure.

NN-Dimethylaniline, *NN*-dimethyl-*m*- and -*p*-toluidine, *m*-nitro- and *p*-bromo-*NN*-dimethylaniline were purchased. Other substituted dimethylanilines were prepared by methylation of the appropriate aniline with methyl phosphate, the method of Billman *et al.*[14] being

[13] Conant and Kirner, *J. Amer. Chem. Soc.*, 1924, **46**, 232.

[14] Billman, Radike, and Mundy, *J. Amer. Chem. Soc.*, 1942, **64**, 2977; Thomas, Billman, and Davis, *ibid.*, 1946, **68**, 895.

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followed, with slight modifications. Yields after one distillation, together with the physical properties of the pure amine are given in the annexed Table.

Substituent	M. p. or b. p. (mm.)	M. p. of picrate	Yield (%)	Substituent	M. p. or b. p. (mm.)	M. p. of picrate	Yield (%)
m-Cl	90°/2	144°	70	*p*-OMe	47°	—	70
p-Cl	33°	—	70	5-Cl, 2-OMe [a]	100°/2	190	60
m-Br	126°/14	136	65	2-OMe, 5-OMe [b]	123°/15	186	70
m-F	82°/15	181	45	3-Me, 4-Me	102°/19	165	55
p-F	35°	—	45	*NN*-Dimethyl-1-naphthylamine	136°/12	145	85
m-I	34·5°	148	80	*NN*-Dimethyl-2-naphthylamine	45·5°	—	60
o-OMe	93°/6	145	65				
m-OMe	118°/6	144	60				

[a] Found: C, 58·2; H, 7·1. $C_9H_{12}ONCl$ requires C, 58·6; H, 6·5%. [b] Found: C, 66·4; H, 8·4. $C_{10}H_{15}O_2N$ requires C, 66·3; H, 8·3%.

The physical constants noted are in agreement with literature values, with the exception of the picrates of *m*-bromo-, *m*-chloro-, and *m*-iodo-*NN*-dimethylanilines, for which Hodgson and Nicholson [15] give m. p.s 182°, 179°, and 182°, respectively.

p-Ethoxy-*NN*-dimethylaniline, m. p. 34°, was obtained from *p*-ethoxyphenyltrimethylammonium iodide by treatment with sodium hydroxide in boiling pentyl alcohol. 4-Bromo-3-methyl-*NN*-dimethylaniline, m. p. 53—53·5°, was prepared according to von Braun and Kruber.[16] The nitration of *NN*-dimethyl-*p*-anisidine by the method of Hodgson and Crook[17] gave 4-methoxy-3-nitro-*NN*-dimethylaniline together with much dinitration product, but no detectable dinitro-compound was formed when the fuming nitric acid (*d* 1·5) used in the original procedure was replaced by concentrated nitric acid (*d* 1·4). The pure base had m. p. 45·5°.

4-Methyl-3-nitro-*NN*-dimethylaniline, m. p. 35·5°, was prepared by the nitration, under similar conditions, of *NN*-dimethyl-*p*-toluidine. The nitration of *NN*-dimethyl-*o*-anisidine, following the same procedure, gave a crude product from which a more volatile isomer was removed by steam-distillation and small amounts of dinitro-derivatives were removed by virtue of their insolubility in dilute hydrochloric acid. The required 2-methoxy-5-nitro-*NN*-dimethylaniline had m. p. 37·5°. *p*-Iodo-*NN*-dimethylaniline, m. p. 79°, was readily prepared by direct iodination of dimethylaniline in methyl alcohol with iodine and yellow mercuric oxide.

Several halogeno-substituted bases were prepared from commercial samples of the appropriate nitroanilines by conversion into the halogenonitrobenzene by the Sandmeyer reaction followed by reduction ($SnCl_2$) and *N*-methylation of the resulting aniline with methyl phosphate:

Substituents	M. p.	Found (%)	Required (%)
4-Cl, 3-Me	40°	N, 8·2; Cl, 21·3	N, 8·2; Cl, 20·9
3-Cl, 4-Me	33	N, 8·1; Cl, 21·1	N, 8·2; Cl, 20·9
4-Cl, 3-OMe	49	C, 58·7; H, 6·5	C, 58·6; H, 6·5
3-Cl, 4-OMe	63·5	C, 58·5; H, 6·5	C, 58·6; H, 6·5
3-Br, 4-OMe	66·5	N, 6·15; B, 34·6	N, 6·1; Br, 34·7
3-Br, 4-Me	33	N, 6·3; Br, 36·8	N, 6·5; Br, 37·3

Other disubstituted bases were obtained by successive reduction and *N*-methylation of the corresponding nitrobenzenes which were synthesised as outlined below. The properties of the purified dimethylanilines are listed in the following table.

Substituents	M. p. or b. p. (mm.)	M. p. of picrate	Found (%)	Required (%)
3-F, 4-OMe	28°	145°	C, 63·3; H, 7·2	C, 63·9; H, 7·2
5-F, 2-OMe	98°/13	164	C, 63·7; H, 7·4	C, 63·9; H, 7·2
3-Cl, 2-OMe	110°/13	133	C, 58·9; H, 6·6	C, 58·6; H, 6·5
2-OMe, 5-Me	120°/23	194	C, 72·4; H, 9·2	C, 72·7; H, 9·2
3-OMe, 4-OMe	41·5°	—	C, 66·5; H, 8·3	C, 66·3; H, 8·3
5-I, 2-OMe	34·5°	191	N, 4·8; I, 45·3	N, 5·0; I, 45·8
3-I, 4-OMe	54°	—	N, 4·8; I, 45·0	N, 5·0; I, 45·8
3-Me, 5-Me	98°/14	186	—	—
3-Cl, 5-Me	124°/14	174	C, 63·9; H, 7·2	C, 63·7; H, 7·1
3-Br, 5-Me	140°/15	182	N, 6·8; Br, 36·8	N, 6·5; Br, 37·3
3-Cl, 5-OMe	29°	—	C, 58·3; H, 6·5	C, 58·6; H, 6·5 [a]
3-Br, 5-OMe	30°	—	N, 6·1; Br, 34·7	N, 6·1; Br, 34·7
3-OMe, 5-Me	116°/6	—	C, 73·0; H, 9·2	C, 72·7; H, 9·2

[a] Calculated values (*i.e.*, not a new compound).

[15] Hodgson and Nicholson, *J.*, 1941, 766.
[16] von Braun and Kruber, *Ber.*, 1913, **46**, 3468.
[17] Hodgson and Crook, *J.*, 1932, 1812.

5-Fluoro-2-methoxy-1-nitrobenzene, m. p. 61°, and 3-fluoro-4-methoxy-1-nitrobenzene, m. p. 104°, were prepared by the nitration of *p*-fluoroanisole and *o*-fluoroanisole respectively (method of Elderfield *et al.*[18]). The similar nitration of *o*-chloroanisole gave a crude product from which the required 3-chloro-2-methoxynitrobenzene was concentrated by steam-distillation from less volatile isomers. Fractionation under reduced pressure followed by crystallisations from alcohol gave the pure nitro-compound, m. p. 56°.

2-Methoxy-5-methyl-1-nitrobenzene was obtained from *o*-cresol by nitration with dilute nitric acid and subsequent methylation with an excess of methyl sulphate and 10% aqueous potassium hydroxide. 3 : 4-Dimethoxynitrobenzene was readily prepared by nitration of veratrole with diluted nitric acid (1 : 1); in this case, sodium sulphide [19] was a convenient reducing agent for the subsequent preparation of the aniline. The direct iodination of *o*- and of *p*-nitroanisole [2] by overnight stirring with a suspension of iodine in concentrated nitric acid at 15° furnished 5-iodo-2-methoxy-1-nitrobenzene, m. p. 96·5°, and 3-iodo-4-methoxy-1-nitrobenzene, m. p. 94°, in almost the theoretical yield.

3-Bromo- and 3-chloro-5-methoxy-1-nitrobenzene were prepared from 3 : 5-dinitroanisole: Partial reduction of the latter compound with sodium polysulphide gave 3-amino-5-methoxy-1-nitrobenzene in high yield, from which the halogeno-compounds were prepared by the Sandmeyer reaction. Sodium polysulphide was a convenient reagent for the reduction of these compounds to the 3 : 5-disubstituted anilines.

3 : 5-Dimethyl-1-nitrobenzene was prepared from 2 : 4-dimethylaniline by the method of Haller and Adams.[21] However, on addition of a solution of the diazotised 2-amino-3 : 5-dimethyl-1-nitrobenzene to a stirred suspension of cuprous oxide in ice-cold absolute alcohol deamination occurred more cleanly and in higher yield than by the published procedure.

4-Methyl-2-nitroaniline was converted into 3-bromo- and 3-chloro-5-nitrotoluene following the general method of Brynmor Jones and Robinson.[1d]

3-Methoxy-5-nitrotoluene was prepared according to Haworth and Lapworth's instructions [22] from 3-amino-5-nitrotoluene, but several modifications were introduced into published methods for the preparation of the latter compound from *p*-toluidine. Thus the well-known nitration of acetyl-*p*-toluidine with fuming nitric acid gave low yields of the required dinitro-derivative (cf. Brady, Day, and Rolt [23]), and acetyl nitrate was preferred as nitrating agent: the acetyl compound (100 g.) was added gradually to a stirred solution of fuming nitric acid (*d* 1·5; 1 l.) in acetic anhydride (240 c.c.) at 0—10°. The mixture was allowed to reach room temperature, then diluted with water (5 l.), and the solid was removed and washed free from acid. The crude product was hydrolysed by stirring with 50% v/v sulphuric acid at 100° for 30 min. Dilution of the resultant suspension with water (1·5 l.) precipitated most of the 4-amino-3 : 5-dinitrotoluene (90 g., 67%), m. p. 168°, unaltered by crystallisation from alcohol. The dinitrotoluidine (63 g.) was dissolved with cooling in a solution of sodium nitrite (23 g.) in concentrated sulphuric acid (160 c.c.). Glacial acetic acid (160 c.c.) was then added below 15° and the resultant solution of diazonium sulphate was added gradually to a suspension of cuprous oxide (15 g.) in ice-cold absolute alcohol (1 l.). When the reaction was complete, half of the alcohol was distilled off and dilution of the concentrated solution with water (2 l.) then precipitated 3 : 5-dinitrotoluene (41 g., 70%), m. p. 90—90·5°. Partial reduction of the latter compound with the calculated amount of sodium polysulphide gave 3-amino-5-nitrotoluene, m. p. 98°, in 88—92% yield.

4-Chloro-2-methoxy-NN-*dimethylaniline* (Found: C, 58·6; H, 6·6. $C_9H_{12}ONCl$ requires C, 58·6; H, 6·5%), b. p. 124°/12 mm. (picrate, m. p. 131°), was obtained by methylation of the corresponding aniline, which in turn was prepared, in 53% overall yield, from 2-amino-5-nitroanisole. The latter amine (50 g.) was acetylated and then reduced overnight by a refluxing mixture of iron pin-dust (60 g.), concentrated hydrochloric acid (1·5 c.c.), alcohol (200 c.c.), and water (30 c.c.), which had been boiled for 30 min. before addition of the nitro-compound. Most of the alcohol was distilled from the resultant suspension, dilute hydrochloric acid (1 : 1 by volume; 200 c.c.) was added, and the solution was filtered. The acid solution was diazotised

[18] Elderfield, Gensler, Williamson, Griffing, Kupchan, Maynard, Kreysa, and Wright, *J. Amer. Chem. Soc.*, 1946, **68**, 1584.
[19] Fargher, *J.*, 1920, **117**, 865.
[20] Robinson, *J.*, 1916, **109**, 1078.
[21] Haller and Adams, *J. Amer. Chem. Soc.*, 1920, **42**, 1840.
[22] Haworth and Lapworth, *J.*, 1923, **123**, 2982.
[23] Brady, Day, and Rolt, *J.*, 1922, **121**, 526.

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and then treated with a solution of cuprous chloride in concentrated hydrochloric acid at 30° until no diazonium chloride remained, and finally at the b. p. for 30 min. 4-Chloro-2-methoxyaniline (25 g.) was recovered from the neutralised solution by steam-distillation. Distillation under reduced pressure followed by crystallisation from alcohol gave the amine as needles, m. p. 57°.

Grants to the Department from The Distillers Company Limited and from Imperial Chemical Industries Limited (who also furnished generous samples of substituted anilines) are gratefully acknowledged. One of the authors (H. P. C.) is indebted to the University of Hull for a Research Studentship.

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359. *The Reaction of Tertiary Benzyl-amines with Free* tert.-*Butoxy-radicals.*

By R. L. HUANG.

Tertiary benzyl-amines Ph·CH_2·NRR′ are dehydrogenated by free *tert.*-butoxy-radicals to the radicals ·CHPh·NRR′ which then dimerise and disproportionate, to extents depending on the nature of R and R′.

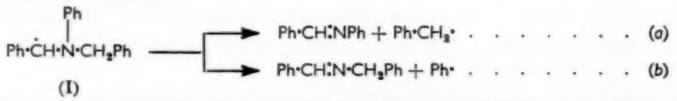
THE reaction of *tert.*-butoxy-radicals with benzyl ethers Ph·CH_2·OR proceeds [1] by abstraction of hydrogen to generate radicals ·CHPh·OR, which then disproportionate into benzaldehyde and the free radical R·, or dimerise, or both, depending on the nature of R. The reaction of the same radicals with tertiary benzyl-amines Ph·CH_2·NRR′, containing a system analogous to that in benzyl ethers, is now reported.

With *tert.*-butyl peroxide as the source of radicals as before, the following benzylamines have been studied: tribenzylamine, dibenzylaniline, dibenzylethylamine, benzylethylaniline, benzyldiphenylamine, and benzyldiethylamine (see Table for a summary of results). Although in general reaction appears to be more complex than with benzyl ethers, the products isolated, which consist of the dimer (II), accompanied in some cases by the anil (III), are best explained as derived from the intermediate aminobenzyl radical ·CHPh·NRR′, analogous to that formed from benzyl ethers, by dimerisation and disproportionation to Ph·CH:NR + R′.

Compared with benzyl ethers the amines, in particular those with alkyl substituents, afford more polymers. These could result from the anils produced, or from unstable enamines such as obtained from tertiary alkylamines and benzoyl peroxide.[2] As evidence for the first possibility it has been found that benzylideneaniline polymerises under the reaction conditions more readily than benzaldehyde, and that, in experiments with tribenzylamine and dibenzylaniline, the yields of anils dropped sharply when a higher molar ratio (1 : 1) of the peroxide was used.

The aminobenzyl radicals also display a somewhat greater tendency towards dimerisation, a process characteristic of more stable radicals. In general, presence of an NPh group favours dimerisation, and enhances the yield of isolable products, whereas progressive substitution by ethyl rapidly increases the complexity of the products.

As with the alkoxybenzyl radicals, the behaviour of the radical ·CHPh·NRR′ depends on the nature of the substituents. Thus disproportionation of the radical (I) could take course (*a*) or (*b*), of which the former is preferred, since the latter would involve generation of the highly energetic phenyl radical.



(I)

[1] Huang and Si-Hoe, *Proc. Chem. Soc.*, 1957, 354; *idem* in " Vistas in Free Radical Chemistry," ed. W. A. Waters, Pergamon Press, London, in the press.
[2] Buckley, Dunstan, and Henbest, *J.*, 1957, 4880, 4901.

For the same reason, the radical ·CHPh·NPh_2 does not disproportionate, but only dimerises.

For reaction of amines with benzoyl peroxide Horner and his co-workers [3] suggest participation of radical intermediates, although Buckley *et al.* prefer an ionic mechanism.[2] Horner [3a] visualises the initial formation of an aminium radical-ion (II) which on loss of a proton gives rise to an aminoalkyl radical, as follows:

$$R{\cdot}CH_2{\cdot}\dot{N}R'R'' + BzO{\cdot} \longrightarrow [R{\cdot}CH_2{\cdot}\dot{N}R'R'']^+BzO^- \text{ (II)} \longrightarrow R{\cdot}\dot{C}H{\cdot}NR'R'' + BzOH$$

If such a radical-ion were first formed, the removal of an α-hydrogen atom as proton in the next step would, in the case of a nuclear-substituted dibenzylamine, depend on the polar nature of the substituent. This does not appear to be supported by recent findings [3b] with monosubstituted dibenzylanilines. With *tert.*-butoxy-radicals we consider that tertiary benzyl-amines undergo dehydrogenation in a manner analogous to that of the benzyl ethers,[1] alkylbenzenes, acids, etc.,[4] and that the reaction does not involve the hetero-atom in the system. However, an attempt to substantiate this by subjecting *N*-benzyl-*N*-*p*-nitrobenzylaniline to reaction with *tert.*-butyl peroxide gave inconclusive results.

Products from reaction of tertiary benzyl-amines with tert.*-butyl peroxide.*[a]

Amine		Products (yield, %)		Amine		Products (yield, %)	
$Ph{\cdot}CH_2{\cdot}NRR'$		Anil	Dimer	$Ph{\cdot}CH_2{\cdot}NRR'$		Anil	Dimer
R	R′	$Ph{\cdot}CH{:}NR$	$[Ph{\cdot}CH{\cdot}NRR']_2$	R	R′	$Ph{\cdot}CH{:}NR$	$[Ph{\cdot}CH{\cdot}NRR']_2$
Ph	Ph	—	40 [b]	$Ph{\cdot}CH_2$	$Ph{\cdot}CH_2$	32	4
Ph	$Ph{\cdot}CH_2$	27	37	,,	,,	Trace	0 [c]
,,	,,	Trace	24 [bc]	,,	,,	35	0 [d]
Ph	Et	0	33	$Ph{\cdot}CH_2$	Et	0	18
				Et	Et	0	0

[a] A 3—4 molar excess of the amine was used, the reaction being carried out in a sealed tube. The yield was calculated on the amine which reacted. [b] Both *meso* and racemic forms isolated. [c] A 1 : 1 molar ratio of amine and peroxide was used. [d] In an open flask under nitrogen.

Experimental

Tribenzylamine.—(*a*) The amine (14·6 g.; m. p. 93°) and *tert.*-butyl peroxide (2·5 g.) were sealed under nitrogen and heated at 100° for 2 days and at 110° for 2 more days. The mixture was extracted with boiling methanol, the solid (0·25 g.) which survived extraction being αβ-*bisdibenzylaminodibenzyl*, m. p. 252—254° (from benzene) (Found: C, 88·4; H, 7·1; N, 5·0. $C_{42}H_{40}N_2$ requires C, 88·1; H, 7·0; N, 4·9%). The methanolic extract, when chilled, deposited unchanged tribenzylamine (4·4 g.; m. p. and mixed m. p.) which was filtered off. The filtrate was concentrated, filtered from a small crop of the above dibenzyl (0·05 g.), then distilled to give the following fractions: (i) material, b. p. 130—140°/0·5 mm. (1·5 g.), n_D^{24} 1·5919; (ii) tribenzylamine, b. p. *ca.* 160°/0·5 mm. (3·4 g.), m. p. and mixed m. p. 93°; and (iii) a brown residue (2·9 g.). Fraction (i) was mostly *N*-benzylidenebenzylamine (32%, calc. on amine which reacted). It gave an immediate precipitate of benzaldehyde 2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p.) with Brady's reagent, and on further distillation had b. p. 118—122°/0·5 mm., n_D^{24} 1·5931 (lit.,[5] $n_D^{17.5}$ 1·6011) (Found: C, 86·1; H, 6·9; N, 6·8. Calc. for $C_{14}H_{13}N$: C, 86·1; H, 6·7; N, 7·1%). A portion (0·4 g.) was hydrogenated in ethanol over Raney nickel, 40 c.c. of hydrogen being absorbed in 30 min., to give dibenzylamine, b. p. 130° (bath)/0·3 mm. 0·24 g., n_D^{22} 1·5730 (lit., n_D^{22} 1·5743), which formed a benzoyl derivative, m. p. and mixed m. p. 113—115°.

(*b*) With a 1 : 1 molar ratio of amine and peroxide, only unchanged amine and polymer, and traces of the anil (as detected by Brady's reagent), were obtained.

(*c*) The reactants were heated under reflux in an atmosphere of nitrogen at 110° for 4 days, to give unchanged amine (70%) and *N*-benzylidenebenzylamine (35%), no dimer being encountered.

[3] (*a*) Horner, *Angew. Chem.*, 1950, **62**, 359; (*b*) Horner and Kirmse, *Annalen*, 1955, **597**, 48, and earlier papers.

[4] *E.g.*, Farmer and Moore, *J.*, 1951, 131; Huang and Morsingh, *J.*, 1953, 160; Huang and Kum Tatt, *J.*, 1954, 2570; 1955, 4229.

[5] Mignonac, *Ann. Chim.* (*France*), 1934, **2**, 225.

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Dibenzylaniline.—(*a*) The amine (13·2 g., m. p. 67°) and *tert.*-butyl peroxide (1·8 g.) were sealed and heated as before, and the resulting mixture was extracted with boiling methanol. The solid which remained was racemic αβ-*bisbenzylphenylaminodibenzyl*, m. p. *ca.* 210° (1·8 g., 37%) raised to 223—225° by recrystallisation from benzene–ethanol from which it separated in stout rods (Found: C, 88·3; H, 6·65. $C_{40}H_{36}N_2$ requires C, 88·2; H, 6·7%). The methanolic extract, after decantation from a brown viscous oil (0·5 g.), gradually deposited unchanged amine (6·8 g.) which was collected. The filtrate was concentrated and distilled, giving volatile material and the following fractions: (i) Benzylideneaniline, b. p. 106—112°/0·5 mm. (0·85 g., 27%) (an authentic sample had b. p. 104—106°/0·2 mm.); (ii) unchanged amine, b. p. 152—161°/0·5 mm. (1·6 g.), m. p. and mixed m. p. 67°; and (iii) a small residue (*ca.* 0·5 g.). Fraction (i) crystallised when seeded with benzylideneaniline, and after recrystallisation from aqueous ethanol had m. p. 45°, alone or mixed with an authentic sample (m. p. 52°). Further recrystallisation, however, did not raise the m. p. A portion (0·42 g.), hydrogenated in ethanol over Raney nickel, absorbed 42 c.c. of hydrogen in 2·5 hr. to give benzylaniline, identified as the benzoyl derivative (*ca.* 0·2 g.), m. p. 104—105°, alone or with an authentic sample of m. p. 107°.

(*b*) The amine (7·0 g., 0·026 mole) and the peroxide (3·8 g., 0·026 mole), heated as above, gave racemic αβ-bisbenzylphenylaminodibenzyl (1·13 g.) and the meso-*isomer*, which was relatively insoluble in benzene, and crystallised from ethyl acetate in rectangular prisms, m. p. 242—245° (0·27 g.) (Found: C, 88·3, 88·3; H, 6·6, 6·7%) (total yield of dimers, 24%). The methanolic extract afforded no crystalline material, and on chromatography (light petroleum on alumina) followed by distillation gave only small quantities of unchanged amine (0·6 g.) and intractable oils. No benzylideneaniline was isolated, although its presence could be detected by means of Brady's reagent, with which it formed benzaldehyde 2 : 4-dinitrophenylhydrazone.

(*c*) Heating the reaction mixture at 90—100° for 4 days resulted in a 84% recovery of the amine, and a 19% yield of the racemic dimer.

Benzylideneaniline (20 g.) and the peroxide (4·0 g.) after the usual treatment gave unchanged anil (12 g.) and a tar, chromatography of which afforded only intractable oils.

Dibenzylethylamine.—The amine (15·0 g., n_D^{22} 1·5562) and *tert.*-butyl peroxide (2·5 g.), after being heated as above, were distilled through a 6-cm. Vigreux column, to give volatile material, unchanged amine (8·4 g.; b. p. 100—101°/0·05 mm., n_D^{22} 1·5578), and a viscous residue (4·0 g.), but no *N*-benzylidene-ethylamine. The residue, on chromatography on alumina in light petroleum, gave the fractions: (i) material (1·4 g.) which on evaporative distillation gave unchanged amine (0·50 g.) and αβ-*bis*(*benzylethylamino*)*dibenzyl*, b. p. 170—190° (bath)/0·05 mm. (0·54 g.), which crystallised in contact with ethanol and had m. p. 121—130°, raised to 127·5—130° after further crystallisations from ethanol–benzene (Found: C, 85·6; H, 7·9; N, 6·3. $C_{32}H_{36}N_2$ requires C, 85·7; H, 8·1; N, 6·2%); (ii) an oil (0·8 g.) which on distillation gave more unchanged amine (0·13 g.), the dibenzyl above (0·55 g.), and a small residue; (iii) small fractions of intractable liquids.

N-*Benzyl*-N-*ethylaniline.*—The amine (19·0 g.; n_D^{24} 1·5937) and the peroxide (3·4 g.) were heated at 110—115° for two days. Fractionation with a 10-cm. Vigreux column then gave volatile material, unchanged peroxide (0·7 g.), unchanged amine (14·3 g.), and a viscous residue, there being no intermediate fraction between the unused peroxide and amine. The residue, adsorbed on alumina and eluted with petroleum, gave fractions: (i) yellow liquid (1·3 g.) which on distillation afforded more unchanged amine (0·55 g.) and a residue which in contact with methanol deposited αβ-*bis*(*ethylanilino*)*dibenzyl*, needles (from methanol), m. p. 124° (0·31 g.) (Found: C, 85·9; H, 7·5; N, 6·4. $C_{30}H_{32}N_2$ requires C, 85·7; H, 7·6; N, 6·7%); (ii) the same dibenzyl (1·1 g.); and four further fractions of oil.

Benzyldiphenylamine.—The amine (12·5 g.; m. p. 89—90°) and the peroxide (3·6 g.) were heated at 125—131° for 25 hr. The mixture soon darkened and, after *ca.* 4 hours' heating, crystals separated. The almost black reaction mixture was extracted with boiling ethanol (*ca.* 80 c.c.), and the solid which remained was recrystallised from benzene to give meso-αβ-*bisdiphenylaminodibenzyl*, prisms decomp. ~264°, m. p. 281° (0·29 g.) (Found: C, 88·6; H, 6·4; N, 5·3. $C_{36}H_{32}N_2$ requires C, 88·4; H, 6·2; N, 5·4%). The ethanol extract, on cooling, yielded (i) a sticky green solid (*ca.* 1·5 g. of impure starting material), (ii) crystals A (9·9 g.), and (iii) more unchanged amine (0·2 g.). Solid A was mainly unchanged amine, and on treatment with boiling ethanol (25 c.c.) mostly dissolved, leaving racemic αβ-*bisdiphenylaminodibenzyl*, which was soluble in benzene but only slightly so in ethanol, and crystallised from a mixture of these

solvents in stout rods, m. p. 222—223° (0·1 g.) (Found: C, 88·4, 88·5; H, 6·4, 6·2%). A solution of the *meso*-isomer in chloroform slowy became dark green.

Benzyldiethylamine and N-*Benzyl*-N-p-*nitrobenzylaniline*.—Only unchanged amine and intractable oils were obtained after similar reactions with these bases.

Thanks are expressed to Dr. W. A. Waters, F.R.S., for a helpful discussion and for his interest in this work during the author's study-leave in Oxford.

UNIVERSITY OF MALAYA, SINGAPORE. [*Received, November 24th*, 1958.]

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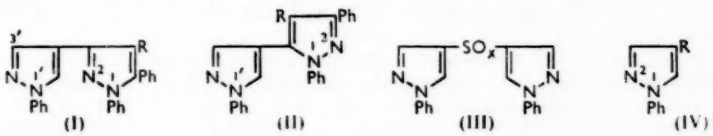
360. *The Preparation of Some Pyrazole Derivatives.*

By I. L. FINAR and G. H. LORD.

Various pyrazoles have been formylated, and these derivatives oxidised to the corresponding acids. Thionyl chloride reacts directly with 1-phenylpyrazole to give the dipyrazolyl sulphoxide which has been oxidised to the sulphone. 4-Formyl-1-phenylpyrazole gives the expected alcohols with Grignard reagents, except that ethylmagnesium halide gave 4-propenyl-1-phenylpyrazole and a dimer. The alcohols have been oxidised to the ketones, and some of these reduced to alkyl compounds by the Clemmensen method. Both 4-formyl-1-phenylpyrazole and 1-phenylpyrazole-4-carboxylic acid have been reduced by lithium aluminium hydride to 4-hydroxymethyl-1-phenylpyrazole. Two bipyrazolyls and one terpyrazole have also been prepared.

DIMETHYLFORMAMIDE and phosphoryl chloride [1] have been used to formylate 1-phenyl- and 1-methyl-pyrazole, but these reagents failed with pyrazole and 1-benzoyl- and 1-benzenesulphonyl-pyrazole.[2] It has now been shown that formylation fails with 1-*p*-nitrophenyl- and 1-(2 : 4-dinitrophenyl)-pyrazole,[3] and with 1 : 5 : 1′-triphenyl-3 : 4′-bipyrazolyl (I; R = H), but is successful with 1-*m*-nitrophenylpyrazole,[3] giving the 4-formyl derivative and with 1 : 3 : 1′-triphenyl-5 : 4′-bipyrazolyl (II; R = H) to give (II; R = CHO). Both formyl compounds, on oxidation, give the corresponding acids. Thionyl chloride [4] has been used instead of phosphoryl chloride, and when this reaction was carried out with 1-phenylpyrazole, only di-(1-phenyl-4-pyrazolyl) sulphoxide (III; $x = 1$) was obtained. This compound was also formed in the absence of dimethylformamide and, on oxidation, was converted into the sulphone (III; $x = 2$). The formation of the sulphoxide by the direct action of thionyl chloride is interesting since in the sulphoxide preparations from thionyl chloride previously investigated Friedel–Crafts conditions have been used.[5]

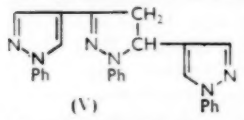


A number of 1-phenyl-4-pyrazolylalkanols were prepared by reaction between 4-formyl-1-phenylpyrazole and the appropriate Grignard reagent (see Table 1). Some of these were oxidised in acetone solution with acid dichromate to the corresponding ketones (see Table 2). Under the same conditions, 2-methyl- and 2 : 2-dimethyl-1-4′-pyrazolylpropan-1-ol gave 1-phenylpyrazole-4-carboxylic acid,[6] but at 5—10° the corresponding ketones

[1] Campaigne and Archer, *J. Amer. Chem. Soc.*, 1953, **75**, 989.
[2] Finar and Lord, *J.*, 1957, 3314.
[3] Finar and Hurlock, *J.*, 1957, 3024.
[4] Smith, *J.*, 1956, 3842.
[5] Schönberg, *Ber.*, 1923, **56**, 2275; Smiles and Le Rossignol, *J.*, 1906, 696; Colby and McLoughlin, *Ber.*, 1887, **20**, 195; Loth and Michaelis, *Ber.*, 1894, **27**, 2547.
[6] Finar and Godfrey, *J.*, 1954, 2293.

were obtained. A few of these ketones have been reduced with amalgamated zinc and hydrochloric acid to the corresponding 4-alkyl derivatives (Table 3). Attempts to reduce 4-formyl-1-phenylpyrazole under the same conditions resulted in a resin. Reduction of the 4-formyl compound and of the 4-carboxylic acid with lithium aluminium hydride produced 4-hydroxymethyl-1-phenylpyrazole,[6] and this was converted into di-(1-phenyl-4-pyrazolyl)methane [6] when heated with 1-phenylpyrazole, phosphoric acid, and dilute acetic acid.

All attempts to isolate 1-(1-phenyl-4-pyrazolyl)propane-1-ol on reaction between ethylmagnesium iodide and 4-formyl-1-phenylpyrazole failed; the products were 4-propenyl-1-phenylpyrazole and a dimer which may be *trans*-3 : 4-di-(1-phenyl-4-pyrazolyl)hex-3-ene. These could be formed from 1-(1-phenyl-4-pyrazolyl)propan-1-ol which is produced first. The presence of this alcohol in the reaction mixture was shown by the isolation of some ethyl pyrazolyl ketone when the crude Grignard reaction product was oxidised. Reduction of this ketone with sodium borohydride gave an oil which was shown to contain the alcohol, but a pure specimen of the latter could not be isolated.



(V)

Ketones were prepared by condensing acetophenone with 4-formyl-1-phenylpyrazole, and benzaldehyde and 4-formyl-1-phenylpyrazole with 4-acetyl-1-phenylpyrazole. Each was condensed with phenylhydrazine, forming the 4 : 5-dihydro-derivatives of compounds (II) and (I), and the dipyrazolylpyrazoline (V). All three pyrazolines were oxidised to the corresponding pyrazoles by potassium permanganate in pyridine.

Experimental

4-Formyl-1-m-nitrophenylpyrazole.—A mixture of 1-*m*-nitrophenylpyrazole [3] (4·25 g., 0·022 mole), dimethylformamide (9·1 g., 0·125 mole), and phosphoryl chloride (5·0 g., 0·33 mole) was heated on the steam-bath for 4 hr., poured on ice, and filtered. The precipitate (2·35 g.) was unchanged nitropyrazole. The filtrate was treated with sodium hydroxide solution to pH 4, and after 12 hr. filtered, giving *4-formyl-1-m-nitrophenylpyrazole* (0·45 g., 9%) as colourless needles (from acetone), m. p. 180° (Found: C, 55·3; H, 3·5; N, 19·2. $C_{10}H_7O_3N_3$ requires C, 55·4; H, 3·2; N, 19·3%).

4-Formyl-1 : 3 : 1′-triphenyl-5 : 4′-bipyrazolyl (II; R = CHO).—A mixture of 1 : 3 : 1′-triphenyl-5 : 4′-bipyrazolyl (II; R = H) (1·5 g., 0·004 mole), dimethylformamide (5·4 g., 0·074 mole), and phosphoryl chloride (1·67 g., 0·011 mole) was treated as above, but in this case the precipitate was the *formylbipyrazolyl* (the filtrate gave only a negligible amount). This, on crystallisation from ethanol and then benzene–light petroleum (b. p. 40—60°), gave needles (1·35 g., 83%), m. p. 169—169·5° (Found: C, 76·5; H, 4·7; N, 14·8. $C_{25}H_{18}ON_4$ requires C, 77·0; H, 4·6; N, 14·4%).

Oxidation of the Formyl Compounds.—The formylnitropyrazole, on oxidation with hot alkaline potassium permanganate solution, gave colourless needles of *1-m-nitrophenylpyrazole-4-carboxylic acid* (from aqueous ethanol), m. p. 253—254° (Found: C, 51·3; H, 3·2; N, 17·8. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0; N, 18·0%). A pyridine solution of the formylbipyrazolyl (II; R = CHO) was refluxed with potassium permanganate and, on working up, gave colourless needles of *1 : 3 : 1′-triphenyl-5 : 4′-bipyrazolyl-4-carboxylic acid* (II; R = CO_2H) (from aqueous ethanol), m. p. 212—213° (decomp.) (Found: C, 73·7; H, 4·7; N, 13·9. $C_{25}H_{18}O_2N_4$ requires C, 73·9; H, 4·4; N, 13·8%).

Di-(1-phenyl-4-pyrazolyl) Sulphoxide (III; $x = 1$).—A mixture of 1-phenylpyrazole (5·8 g., 0·04 mole) and thionyl chloride (14·0 g., 0·13 mole) was refluxed for 3 hr., the excess of thionyl chloride evaporated, and the cooled solution then poured into water (150 c.c.). The precipitate was collected, washed with water, and recrystallised from acetone, to give colourless plates of the *sulphoxide* (1·0 g., 14·5%), m. p. 154° (Found: C, 64·5; H, 4·1; N, 16·8; S, 9·7. $C_{18}H_{14}ON_4S$ requires C, 64·7; H, 4·2; N, 16·75; S, 9·6%).

Di-(1-phenyl-4-pyrazolyl) Sulphone (III; $x = 2$).—The sulphoxide (3·1 g.), acetic acid (60 c.c.), and 100-vol. hydrogen peroxide (40 c.c.) were heated on the steam-bath for 3 hr., then

poured into water (200 c.c.). The precipitate was collected, washed with water, and recrystallised from ethanol, to give colourless plates of the *sulphone* (2·4 g.; 74%), m. p. 180° (Found: C, 61·6; H, 4·3; N, 15·9; S, 8·9. $C_{18}H_{14}O_2N_4S$ requires C, 61·75; H, 4·0; N, 16·0; S, 9·1%).

1-(1-*Phenyl*-4-*pyrazolyl*)*ethanol*.—To methylmagnesium iodide (magnesium, 3·39 g., 0·139 mole; methyl iodide, 19·6 g., 0·139 mole) in ether (100 c.c.) was added dropwise 4-formyl-1-phenylpyrazole (20·0 g., 0·116 mole) in benzene (300 c.c.) during 1 hr. with stirring. The mixture was gently refluxed for a further 2 hr., cooled, and hydrolysed by the dropwise addition of 25% ammonium chloride solution (100 c.c.). The benzene–ether layer was separated from the aqueous layer which was extracted with ether (3 × 100 c.c.). The benzene solution and ethereal extracts were combined, washed with water, dried (Na_2SO_4), and evaporated. The residual red oil was extracted with hot ligroin (b. p. 100—120°) which, on evaporation, left a pale yellow oil (20·6 g.). This was distilled rapidly and the fraction (9·3 g.), b. p. 172—176°/0·06 mm., was redistilled to give the *pyrazolylethanol* (7·8 g., 53·3%), b. p. 152—153°/0·04 mm. (Found: C, 70·6; H, 6·35; N, 15·2. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%). The other alkanols (see Table 1) were similarly prepared, in 49—79% yield (no extraction with ligroin was used for these compounds).

TABLE 1.

Alkanol (IV) R =	Halide for Grignard	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
CHPr^n·OH	PrI	73·5—74° *	72·5	7·45	13·1	$C_{13}H_{16}ON_2$	72·2	7·4	13·0
CHPr^i·OH	Pr^{i}I	75·5—76 †	72·4	7·3	13·0				
CHBu^n·OH	Bu^{n}Br	68—69 *	73·1	7·7	12·2	$C_{14}H_{18}ON_2$	73·1	7·8	12·15
CHBu^t·OH	Bu^{t}Cl	99—99·5 *	72·8	7·9	12·4				
CHPh·OH	PhBr	120—121 *	76·5	5·6	11·5	$C_{16}H_{14}ON_2$	76·8	5·6	11·2

* Recrystallised from aqueous methanol. † Recrystallised from benzene–light petroleum.

4-*Acetyl*-1-*phenyl*-4-*pyrazole*.—1-(1-Phenyl-4-pyrazolyl)ethanol (IV; 5·4 g.) in acetone (25 c.c.) was added slowly, with stirring, to cold acid dichromate solution (150 c.c.; 100 g. of sodium dichromate, 250 c.c. of concentrated sulphuric acid, 750 c.c. of water). The temperature of the mixture was not allowed to exceed 50°. After ½ hr., the solution was diluted with water, and the precipitate collected, washed with water, and recrystallised from ethanol to give the ketone (4·85 g., 91%), m. p. 129° (Balbiano [7] gives m. p. 121·5—122·5°). The other ketones (see Table 2) were similarly prepared, in 69—87% yield (the temperature was kept between 5—10° for the first, second, and fifth).

TABLE 2.

Ketone (IV) R =	M. p.*	Found (%) C	H	N	Formula	Required (%) C	H	N
Ac	109—109·5°	71·6	5·9	13·9	$C_{12}H_{12}ON_2$	72·0	6·0	14·0
COPr^n	114	72·7	6·4	12·9	$C_{13}H_{14}ON_2$	72·9	6·5	13·1
COPr^i	117·5—118	72·3	6·5	12·8				
COBu^n	110·5—111·5	73·6	7·0	12·5	$C_{14}H_{16}ON_2$	73·7	7·0	12·3
COBu^t	99·5—100	73·8	6·9	12·1				
Bz	126—126·5 †							

* All compound recrystallised from aqueous ethanol. † Balbiano [7] gives m. p. 123°.

Clemmensen Reduction of the Ketones.[8]—Freshly prepared amalgamated zinc (10 g.) and the ketone (0·01 mole) were refluxed for 2 hr. with 5N-hydrochloric acid (15 c.c.), further acid (12 c.c.) being added during this period. When cool, the solution was decanted from the zinc residue, the latter was washed with water and then ether, and the decanted liquid and washings were combined, saturated with sodium chloride, and extracted with ether (3 × 75 c.c.). The ethereal extract was dried (Na_2SO_4), the ether evaporated, and the residual oil distilled *in vacuo*, to give the 4-*alkyl*-1-*phenylpyrazoles* in 42—59% yield (Table 3).

Attempted Preparation of **1-(1-*Phenyl*-4-*pyrazolyl*)*propan*-1-*ol*.**—4-Formyl-1-phenylpyrazole (15 g.) was added to ethylmagnesium iodide (31·45 g.) as described above for the pyrazolylethanol. The oil obtained on evaporation of the benzene–ether solvent was extracted with cold light petroleum (400 c.c.) which was then chromatographed on alumina. The mother-liquor

[7] Balbiano, *Gazzetta*, 1889, **19**, 128.
[8] Clemmensen, *Ber.*, 1914, **47**, 51; Brewster and Harris, *J. Amer. Chem. Soc.*, 1930, **52**, 4886.

TABLE 3.

Alkylpyrazole (IV) R =	B. p./mm.	Found (%) C	H	N	Formula	Required (%) C	H	N
CHEt	102—103°/0·5	77·2	7·0	16·3	$C_{11}H_{13}N_2$	76·8	7·0	16·3
Pr^n	133—134°/0·6	77·6	7·2	15·1	$C_{12}H_{14}N_2$	77·4	7·5	15·1
Bu^n	136—137°/0·7	78·1	7·8	14·0	$C_{13}H_{16}N_2$	78·0	8·0	14·0
n-C_5H_{11}	150—152°/0·9	78·5	8·3	13·2	$C_{14}H_{18}N_2$	78·5	8·4	13·1

(of light petroleum) gave, on evaporation, a liquid which, on cooling to 0°, solidified. When the temperature was raised to 20° some solid melted. The fine white needles of 1-*phenyl*-4-*propenylpyrazole* had m. p. 39—40° (Found: C, 78·4; H, 6·2; N, 15·4. $C_{12}H_{12}N_2$ requires C, 78·3; H, 6·5; N, 15·2%). A chloroform solution of the pure compound rapidly absorbed bromine, and on oxidation with acid dichromate at 0—5° gave 1-phenylpyrazole-4-carboxylic acid. The infrared spectrum of the propenylpyrazole was similar to that of 1-phenyl-4-propylpyrazole, the main difference being the presence in the former of a shoulder at 966 cm.$^{-1}$; this shoulder, which is quite pronounced, has been assigned to a CH out-of-plane deformation frequency in a *trans*-disubstituted ethylene group since such a structure is known to give a strong absorption band at 970—960 cm.$^{-1}$.[9]

When, instead of extraction with light petroleum, the product (oil) was distilled, the small fraction of b. p. 110—112°/0·05 mm. gave, on oxidation at 0—5°, 1-phenylpyrazole-4-carboxylic acid. The non-volatile residue was chromatographed in ligroin on alumina. Elution with benzene, followed by evaporation of the solvent, gave a solid, m. p. 104—105° (Found: C, 78·1; H, 6·45; N, 15·2%). Molecular-weight determination cryoscopically in benzene showed it to be a dimer of the propenylpyrazole. This dimer absorbed half the amount of bromine required for the monomer, and oxidation at 50° gave 1-phenyl-4-propionylpyrazole and 1-phenylpyrazole-4-carboxylic acid. The structure 3 : 4-di-(1-phenyl-4-pyrazolyl)hex-3-ene is in keeping with these results and is supported by absorption bands in the 1680—1620 cm.$^{-1}$ region, thereby indicating symmetrical (*trans*-)tetrasubstitution [9] of the type $(CRR')_2$.

Since attempts to isolate the pyrazolylpropanol as a derivative failed, the crude alkanol was oxidised to the ketone (see Table 2) which was then reduced by sodium borohydride [10] to a yellow oil which was too impure to give a correct analysis, but its infrared spectrum was very similar to that of 1-(1-phenyl-4-pyrazolyl)ethanol. One impurity in this compound was 1-phenyl-4-propenylpyrazole since there was a shoulder at 966 cm.$^{-1}$.

4-*Hydroxymethyl*-1-*phenylpyrazole*.[6]—This was prepared by reducing 4-formyl-1-phenylpyrazole (77% yield) or 1-phenylpyrazole-4-carboxylic acid (81% yield) with an excess of lithium aluminium hydride.[11] Reduction of the formyl compound with sodium borohydride [10] gave a yield of 81%.

Di-(1-*phenyl*-4-*pyrazolyl*)*methane*.[6]—4-Hydroxymethylpyrazole (2·55 g., 0·015 mole), 1-phenylpyrazole (4·2 g., 0·03 mole), glacial phosphoric acid (7·5 c.c.), glacial acetic acid (15 c.c.) and water (15 c.c.) were heated on the steam-bath for 12 hr., then cooled, diluted with water (75 c.c.), and set aside for 12 hr. The precipitate was collected, washed with water, and recrystallised from methanol (charcoal), to give the dipyrazolylmethane (53·5%), m. p. 113—114°.

Propenones.—4-Formyl-1-phenylpyrazole (30 g., 0·175 mole) in ethanol (200 c.c.) was added dropwise, with stirring, to a cooled solution of sodium hydroxide (12 g., 0·52 mole) [in water (80 c.c.) and ethanol (40 c.c.)] and acetophenone (21 g., 0·175 mole) at 10—15°. The mixture was kept for 12 hr., and the solid then collected, washed well with water, dried at 110°, and recrystallised twice from benzene–light petroleum, to give needles of 1-*phenyl*-3-(1-*phenyl*-4-*pyrazolyl*)*prop*-2-*en*-1-*one* (*A*) (38·9 g., 57%), m. p. 181° (Found: C, 78·5; H, 5·3; N, 9·8. $C_{18}H_{14}ON_2$ requires C, 78·8; H, 5·1; N, 10·2%). In the same way, 4-acetyl-1-phenylpyrazole and benzaldehyde gave 4-*cinnamoyl*-1-*phenylpyrazole* (*B*) (47%), m. p. 170·5—171·5° (from benzene) (Found: C, 78·4; H, 5·1; N, 10·2%); 4-acetyl-1-phenylpyrazole and 4-formyl-1-phenylpyrazole gave 1 : 3-*di*-(1-*phenyl*-4-*pyrazolyl*)*prop*-2-*en*-1-*one* (*C*) (77·5%), m. p. 250—250·5° (from benzene–light petroleum) (Found: C, 74·6; H, 4·7; N, 16·5. $C_{21}H_{16}ON_4$ requires C, 74·2; H, 4·7; N, 16·5%).

Pyrazolines.—Phenylhydrazine (1·6 g., 0·015 mole) in glacial acetic acid (25 c.c.) was added

[9] Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, 2nd edn., 1958, pp. 34 *et seq.*
[10] Chaikin and Brown, *J. Amer. Chem. Soc.*, 1949, **71**, 122.
[11] Nystrom and Brown, *ibid.*, 1947, **69**, 1197.

dropwise to a hot solution of the ketone (*A* in preceding paragraph) (3·69 g., 0·014 mole) in glacial acetic acid (50 c.c.), and the mixture heated for a further hour on the steam-bath. It was kept for 12 hr., and the solid then collected, washed with a little ethanol, and recrystallised from ethanol, to give colourless needles of 1 : 3-*diphenyl*-5-(1-*phenyl*-4-*pyrazolyl*)*pyrazoline* (92%), m. p. 192° (Found: C, 78·8; H, 5·5; N, 15·4. $C_{24}H_{20}N_4$ requires C, 79·1; H, 5·5; N, 15·4%). In the same way, the ketone (*B*) and phenylhydrazine gave 1 : 5-*diphenyl*-3-(1-*phenyl*-4-*pyrazolyl*)*pyrazoline* (76%), m. p. 169—170° (from benzene) (Found: C, 78·8; H, 5·5; N, 15·7%); the ketone (*C*) and phenylhydrazine gave 1-*phenyl*-3 : 5-*di*-(1-*phenyl*-4-*pyrazolyl*)-*pyrazoline* (53%), m. p. 227—228° (from chloroform–light petroleum) (Found: C, 75·6; H, 5·1; N, 19·2. $C_{27}H_{22}N_6$ requires C, 75·3; H, 5·1; N, 19·5%). All three pyrazolines gave a blue fluorescence under ultraviolet light.

Pyrazolyls.—A mixture of the 4 : 5-dihydro-derivative of the bipyrazolyl (II; R = H) (3·65 g.), powdered potassium permanganate (3 g.), pyridine (20 c.c.), and water (5 c.c.) was kept for 1·5 hr., then heated at 100° for 20 min. The solid isolated was recrystallised from benzene–light petroleum, to give needles of 1 : 3 : 1′-*triphenyl*-5 : 4′-*bipyrazolyl* (II; R = H) (55%), m. p. 109—110° (Found: C, 79·3; H, 5·2; N, 15·2. $C_{24}H_{18}N_4$ requires C, 79·6; H, 5·0; N, 15·45%). In the same way, the 4 : 5-dihydro-derivative of the bipyrazolyl (I; R = H) gave 1 : 5 : 1′-*triphenyl*-3 : 4′-*bipyrazolyl* (I; R = H) (97%), m. p. 166·5—167° (from aqueous ethanol) (Found: C, 79·3; H, 5·0; N, 15·4%). 1-*Phenyl*-3 : 5-*di*-(1-*phenyl*-4-*pyrazolyl*)*pyrazole* (69%), m. p. 167·5—168° (from benzene–light petroleum) (Found: C, 75·9; H, 4·7; N, 19·3. $C_{27}H_{20}N_6$ requires C, 75·6; H, 4·7; N, 19·6%), was similarly prepared.

We thank Mr. Pyszora of the National College of Rubber Technology for the spectroscopic data.

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LONDON, N.7.

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361. *Griseofulvin. Part XIV.* Some Alcoholytic Reactions and the Absolute Configuration of Griseofulvin.*

By J. MACMILLAN.

Racemisation of the asymmetric spiran centre of griseofulvin takes place on treatment with 0·5N-sodium methoxide, and probably with 0·04N-sodium ethoxide. In contrast, the corresponding trione (II; R = R′ = Me) is stable to both 0·5N-sodium methoxide and ethoxide. In both compounds sodium ethoxide causes replacement of methoxyl by ethoxyl groups.

The absolute configuration of griseofulvin is deduced as (2*S* : 6′*R*)-7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione.

IN Part IV [1] of this series some alcoholytic reactions of griseofulvin (I; R = R′ = R″ = Me) and of the parent trione (II; R = R′ = Me) were mentioned briefly. Further investigation of these reactions is now reported.

The product, m. p. 239—240°, obtained [1] from griseofulvin and boiling 0·5N-sodium methoxide was found to be a mixture of griseofulvin (40%) and a diastereoisomer (60%). This mixture was separated by chromatography on alumina or by fractional crystallisation of the mixed triones obtained by acid hydrolysis. Methylation of the diastereoisomeric trione (II; R = R′ = Me) afforded the diastereoisomer of griseofulvin and of the isomeric enol ether (III; R = R′ = R″ = Me).

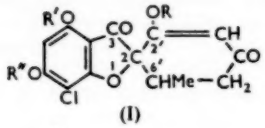
The constitution of the diastereoisomer of griseofulvin was established as follows. First, it was converted by boiling 0·5N-sodium methoxide into griseofulvin *via* the above diastereoisomeric mixture. Secondly, oxidation with zinc permanganate [2] to the acid (IV),

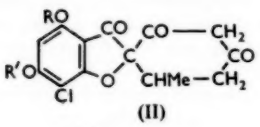
* Part XIII, *J.*, 1958, 2929.

[1] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3977.
[2] Grove, Ismay, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3958.

and periodate cleavage of the latter, gave (+)-methylsuccinic acid which was also obtained from griseofulvin.[3] It follows that the spiran and not the 6′-centre (CHMe) is inverted in the formation of the diastereoisomer.

The acid (IV), as isolated by oxidation of the diastereoisomer, had $[\alpha]_D$ −31° (in ethanol), lowered to −19° by dissolution in 3N-sodium hydroxide and recovery: the acid (IV) from griseofulvin had $[\alpha]_D$ −19° (in ethanol), unchanged by treatment with 3N-sodium hydroxide.


(I)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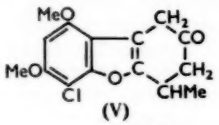
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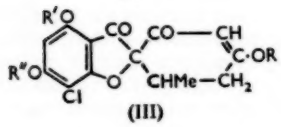
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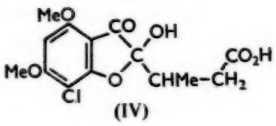
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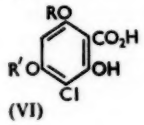
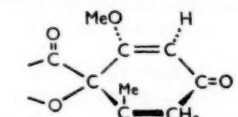
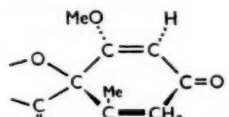

(VI)

Thus the acid (IV), as normally prepared from griseofulvin, appears to be the equilibrium mixture of $C_{(2)}$-diastereoisomers, accounting for the observed formation of two diastereoisomeric lactones.[3]

Since (+)-methylsuccinic acid has been related to D-glyceraldehyde,[4] the absolute configuration at position 6′ in both griseofulvin and the diastereoisomer is fixed as in (VII) and (VIII). The configuration of the spiran centre relative to the 6′-centre may be deduced as follows. From optical-rotation data the equilibrium mixture of diastereoisomers, obtained from both griseofulvin and the diastereoisomer, contains only 40% of griseofulvin. The latter is therefore assigned the sterically less favoured configuration (VII) where the 3-carbonyl and the 6′-methyl groups are *cis*; the diastereoisomer would then be (VIII). On the nomenclature system of Cahn, Ingold, and Prelog,[5] griseofulvin and the diastereoisomer are, respectively, (2*S* : 6′*R*)- and (2*R* : 6′*R*)-7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione. With this system, correlation of configuration in a series of related compounds is not always evident. To overcome this difficulty here and in subsequent papers it is proposed, by agreement with the Editor, to designate the two asymmetric centres by *d* and *l* (though, for bibliography, the *R*,*S* designations will also be noted at appropriate places); thus griseofulvin is prefixed by (*d*,*d*) and the diastereoisomer by (*l*,*d*), the spiran centre being that first mentioned.

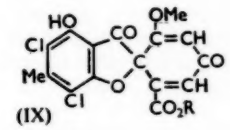

(VII)

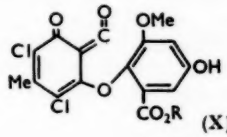

(VIII)

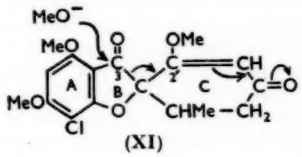
Barton and Scott[6] have reported recently that the spiran centres in geodin (IX; R = H) and erdin (IX; R = Me) are racemised at room temperature in dioxan containing 2% of hydrogen chloride, and these authors suggest a mechanism involving the intermediate keten-ketone (X). In the present case racemisation could proceed by nucleophilic attack of methoxide ion at position 3 (see XI) or at 2′ (see XII). The latter seems less likely since it implies rupture of ring C, and this ring has been shown[1] to survive as orcinol monomethyl ether in the cleavage of griseofulvin by 2N-sodium methoxide.

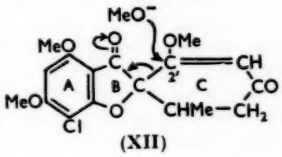
[3] Grove, MacMillan, Mulholland, and Zealley, *J.*, 1952, 3967.
[4] Klyne, "Progress in Stereochemistry," Butterworths, London, 1951, Vol. I, Chapter 5.
[5] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.
[6] Barton and Scott, *J.*, 1958, 1767.

Unlike their methyl ethers, both the (*d*,*d*)- and the (*l*,*d*)-trione (II; R = R′ = Me) are stable to boiling 0·5N-sodium methoxide (cf. usnic acid [7]). With 0·5N-sodium hydroxide the (*l*,*d*)-trione, like the (*d*,*d*)-trione,[8] gave the dibenzofuran (V), although in very low yield. In contrast to (*d*,*d*-I; R = R′ = R″ = Me) which also gives the dibenzofuran (V) with


(IX)


(X)


(XI)


(XII)

0·5N-sodium hydroxide, the (*l*,*d*)-diastereoisomer yielded the salicylic acid (VI; R = R′ = Me); this result may reflect the greater accessibility of the 3-carbonyl group in the (*l*,*d*)-diastereoisomer (see VIII).

In Part IV,[1] the (*d*,*d*)-trione (II; R = R′ = Me) and boiling 0·5N-sodium ethoxide were stated to yield a compound $C_{17}H_{17}O_6Cl$ by replacement of the alkali-labile aryl-methoxyl group by an ethoxyl group. This conclusion has been shown to be incorrect by the non-identity of this product and the (*d*,*d*)-trione (II; R = Me, R′ = Et), derived from the (*d*,*d*)-ethyl ether (I; R = R″ = Et, R′ = Me) of established structure.[9] Further elementary analyses of the alcoholysis product (and methyl and ethyl ethers) established the formula $C_{18}H_{19}O_6Cl$, and alkoxyl determinations confirmed the absence of methoxyl groups but the presence of two ethoxyl groups. These facts suggested structure (II; R = R′ = Et) which was confirmed by oxidation to the salicylic acid (VI; R = R′ = Et). The latter compound was identified by conversion into the ethyl ether ethyl ester, identical with a synthetic specimen prepared by chlorination of ethyl 2 : 4 : 6-triethoxybenzoate. The trione (II; R = R′ = Et) had the same molecular rotation as the (*d*,*d*)-trione (II; R = R′ = Me). Thus treatment of the latter compound with boiling 0·5N-sodium ethoxide replaces both methoxyl groups by ethoxyl without causing racemisation.

Griseofulvin and boiling 0·04N-sodium ethoxide gave a complex mixture. Chromatography of the neutral fraction gave the alcoholysis product, described in Part IV,[1] in low yield but with a higher m. p. (210—212°); the (*d*,*d*)-triethyl ether (I; R = R′ = R″ = Et) and traces of an unidentified substance, m. p. 200°, were also isolated. The acidic fraction, after ethylation and chromatography, gave the (*d*,*d*)-triethyl ether (III; R = R′ = R″ = Et) and an unidentified substance, m. p. 173—175°. The product of m. p. 210—212°, appears to be isomeric with, but possesses half the molecular rotation of, (*d*,*d*)-7-chloro-6 : 2′-diethoxy-4-methoxy-6′-methylgris-2′-en-3 : 4′-dione (I; R = R″ = Et, R′ = Me),[9,10] one of the alternative structures suggested for it in Part IV; [1] it may therefore be a mixture of the (*d*,*d*)- and the (*l*,*d*)-diastereoisomer of (I; R = R″ = Et, R′ = Me).

Experimental

For general experimental details see Duncanson *et al.*[9] In chromatography columns were eluted in ultraviolet light. Unless otherwise stated, ultraviolet absorption spectra were determined for ethanol solutions, and infrared spectra for Nujol mulls.

[7] MacKenzie, *J. Amer. Chem. Soc.*, 1955, **77**, 2214.
[8] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.
[9] Duncanson, Grove, MacMillan, and Mulholland, *J.*, 1957, 3555.
[10] Duncanson, Grove, and Jeffs, *J.*, 1958, 2929.

XUM

(l,d)(i.e., 2R : 6′R)-7-*Chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (I; R = R′ = R″ = Me).—(A) *Preparation of the mixture of* (l,d *and* d,d)-*diastereoisomers.* The (*d*,*d*)-compound (I; R = R′ = R″ = Me) (1·3 g.) was boiled for 5 hr. with sodium (1·5 g.) in methanol (130 ml.). The reaction mixture which had $[\alpha]_D^{17}$ +178° was worked up as described previously,[1] giving the mixture (821 mg.) of (*d*,*d* and *l*,*d*)-isomers (I; R = R′ = R″ = Me); crystallisation from benzene–light petroleum (b. p. 60—80°) gave needles, m. p. 240—242°, $[\alpha]_D^{20}$ +179° (*c* 1·0 in 0·5N-sodium methoxide), +181° (*c* 1·1 in acetone), +202° (*c* 0·96 in chloroform) (Found: C, 57·8; H, 4·9; Cl, 10·0; OMe, 25·8. Calc. for $C_{17}H_{17}O_6Cl$: C, 57·9; H, 4·85; Cl, 10·1; 3OMe, 26·4%), $\nu_{max.}$ 1717, 1705, ~1670, 1655 cm.$^{-1}$, (in ethylidene chloride) 1714 and 1667 cm.$^{-1}$. The specific rotation was unchanged after heating of the product under reflux for a further 20 hr. in 0·5N-sodium methoxide.

(B) *Separation of the diastereoisomeric mixture.* (i) The mixture (2·0 g.) in benzene (150 ml.) was adsorbed on alumina (40 × 1·5 cm.) and eluted with benzene–methanol (199 : 1). In a typical experiment the band fluorescing blue was 26 cm. long and was collected in 13 fractions, comprising a fore-run, then 6 × 1 cm., 5 × 3 cm. and finally 1 × 5 cm. lengths of the band. The following fractions were obtained (specific rotations in chloroform in parentheses): (1) Fore-run 211 mg.; (2) 66 mg.; (3) 48 mg.; (4) 42 mg. (1—4 having $[\alpha]_D$ < +100°); (5) 40 mg. (+111°); (6) 78 mg. (+140°); (7) 128 mg. (+148°); (8) 257 mg. (+162°); (9) 253 mg. (+191°); (10) 173 mg. (+236°); (11) 270 mg. (+274°); (12) 152 mg. (+301°); (13) 182 mg. (+305°).

In this way 18·0 g. were chromatographed in 2·0 g. batches, giving: (*a*) 3·2 g., $[\alpha]_D$ <100°; (*b*) 2·0 g., $[\alpha]_D$ >300°; and (*c*) 11·8 g. of intermediate $[\alpha]_D$; crystallisation of (*b*) from ethanol gave the (*d*,*d*)-isomer (I; R = R′ = R″ = Me) as needles (1·375 g.), m. p. 219—222°, $[\alpha]_D^{20}$ +342° (*c* 1·57 in chloroform). Crystallisation of (*a*) from benzene gave the (*l*,*d*)-diastereoisomer, (2R : 6′R)-7-*chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (I; R = R′ = R″ = Me), in needles (2·64 mg.), m. p. 214—216°, $[\alpha]_D^{22}$ +88° (*c* 0·99 in chloroform), 78° (*c* 0·97 in acetone) (Found: C, 57·5, 57·6; H, 4·85, 4·8; Cl, 10·0; OMe, 25·9. $C_{17}H_{17}O_6Cl$ requires C, 57·9; H, 4·85; Cl, 10·1; 3OMe, 26·4%), $\lambda_{max.}$ 323, 290, ~252, 236 mμ (log ε 3·78, 4·41, 4·25, 4·46), $\nu_{max.}$ 1718 and 1667 cm.$^{-1}$, (in ethylidene chloride) 1719 and 1670 cm.$^{-1}$, (in chloroform) 1718 and 1660 cm.$^{-1}$. The corresponding $\nu_{max.}$ for the (*d*,*d*)-isomer were: 1705 and 1658; 1715 and 1669; 1708 and 1655 cm.$^{-1}$.

A mixture (2 : 3) of the pure (*d*,*d*)- and (*l*,*d*)-diastereoisomers, once crystallised from benzene–light petroleum (b. p. 60—80°), and the mixture of diastereomers, described in (A), had identical infrared spectra. An approximate m. p.–composition curve is shown in the Figure.

(ii) The diastereoisomeric mixture (3·0 g.) in methanol (600 ml.) was hydrolysed with 2N-hydrochloric acid (750 ml.) as described for (*d*,*d*-I; R = R′ = R″ = Me),[8] and the crude solid product (2·7 g.) was extracted with sodium carbonate solution. A solution of the neutral fraction in ether was combined with ether-washings of the sodium carbonate extract; recovery yielded a gum, a warm ether extract of which deposited long needles (63 mg.) of (*l*,*d*)-7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione (III; R = R′ = R″ = Me) (see below).

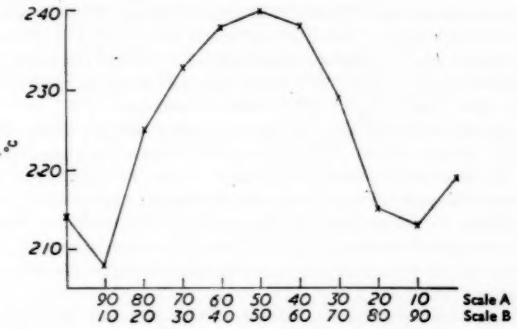
The recovered acidic fraction (1·96 g.), decomp. 250—255°, $[\alpha]_D^{18}$ +227° (*c* 1·08 for the sodium salt in water), was fractionally crystallised from acetic acid, giving (i) the less soluble (*d*,*d*)-7-chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′ : 4′-trione, prisms (305 mg.), decomp. 260—263°, $[\alpha]_D^{18}$ +414° (*c* 1·04 for the sodium salt in water), and (ii) (l,d)(i.e., 2R : 6′R)-7-*chloro*-4 : 6-*dimethoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione* (II; R = R′ = Me), prisms (689 mg.), decomp. 219—223°, $[\alpha]_D^{15}$ +111° (*c* 1·06 for the sodium salt in water) [Found: (sample crystallised from acetic acid and dried over potassium hydroxide at 140°/0·1 cm. for 7 hr.) C, 56·4; H, 4·7; Cl, 10·0; OMe, 17·2%; (sample crystallised from ethyl methyl ketone and dried in the same way) C, 55·6; H, 4·5; Cl, 10·4; OMe, 18·1%; equiv. (phenolphthalein) 346. $C_{16}H_{15}O_6Cl$ requires C, 56·7; H, 4·5; Cl, 10·5; 2OMe, 18·3%, *M*, 338·5]. Consistently low carbon values were obtained irrespective of the mode of preparation or conditions of drying. $\nu_{max.}$ were at 1673, 1605 (broad), 1511, 3195, and 3545 cm.$^{-1}$.

Methylation.—The (*l*,*d*)-trione (100 mg.) was treated with diazomethane. Several crystallisations of the product from methanol gave needles (57 mg.), m. p. 180—185°. Adsorption on alumina (8 × 1·5 cm.) from benzene (5 ml.) and fractional elution with ether–methanol (99 : 1) gave (*a*) (*l*,*d*)-7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione (I; R = R′ = R″ = Me), needles (21 mg.), m. p. 213—215° (from methanol), identified by mixed m. p. and infrared spectrum, (*b*) mixed fractions (20 mg.), m. p. 170—180°, and (*c*) (l,d)(i.e., 2R : 6′R)-7-*chloro*-4 : 6 : 4′-*trimethoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione* (III; R = R′ = R″ = Me), long needles

(7 mg.), m. p. 200—202° (from methanol), $[\alpha]_D^{18}$ +92° (*c* 1·02 in acetone) (Found: C, 57·9; H, 5·0; Cl, 10·3; OMe, 26·0. $C_{17}H_{17}O_6Cl$ requires C, 57·9; H, 4·85; Cl, 10·1; OMe, 26·4%). $\lambda_{max.}$ 325, 290, 262, ~225 mμ (log ε 3·76, 4·35, 4·30, 4·30), $\nu_{max.}$ 1719, 1645, 1608, ~1592, 1506 cm.$^{-1}$

Reactions of (l,d)(i.e., 2R′ : 6′R)-7-*Chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (I; R = R′ = R″ = Me).—(a) *Treatment with* 0·5N-*sodium methoxide.* The compound (50 mg.) was boiled for 4·5 hr. with sodium (57 mg.) in magnesium-dried methanol (50 ml.). Dilution with ice-water gave the mixture of (*d*,*d*)- and (*l*,*d*)-isomers (I; R = R′ = R″ = Me), needles (30 mg.), m. p. 240—242° [from benzene–light petroleum (b. p. 60—80°)], $[\alpha]_D^{19}$ +203° (*c* 0·99 in chloroform), showing infrared absorption identical with that of the mixture obtained from the (*d*,*d*)-isomer.

(b) *Aqueous alkaline hydrolysis.* The compound (215 mg.) was boiled for 4·5 hr. in nitrogen with freshly prepared 0·5N-sodium hydroxide which had previously been boiled for 1 hr. in nitrogen. After filtration from a trace of solid, the alkaline filtrate was extracted with ether, then saturated with carbon dioxide, re-extracted with ether (2 mg. of intractable gum), and acidified. The resultant solid (148 mg.) was collected and sublimed at 160°/10^{-2} mm. Crystallisation of the sublimate from ethyl acetate gave 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid as needles (18 mg.), m. p. 220—222° (decomp.), identified by infrared spectrum and by methylation to the methyl ether methyl ester, m. p. and mixed m. p. 127—128°.



Mixed m. p. diagram for (l,d)- (*scale A*) *and* (d,d)-*griseofulvin* (*scale B*).

(c) *Zinc permanganate oxidation.* The compound (2·88 g.) in acetone (910 ml.) was treated with 2% aqueous zinc permanganate (340 ml.) in five portions during 0·5 hr. After 4 hr. (occasional shaking) excess of permanganate was destroyed with ethanol, and the mixture filtered. The filtrate and acetone washings were worked up as described [2] for the zinc permanganate oxidation of griseofulvin, giving (i) starting material, needles (414 mg.) (from ethanol), m. p. and mixed m. p. 211—213°, (ii) an acidic gum (1·5 g.) which crystallised from ethyl acetate–light petroleum (b. p. 60—80°) in needles (520 mg.), m. p. 181—184° not depressed on admixture with 7-chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid (m. p. 180—184°) obtained from (*d*,*d*)-griseofulvin (Found: C, 51·3, 51·2; H, 4·7, 4·9. Calc. for $C_{14}H_{15}O_7Cl$: C, 50·8; H, 4·6%), $\nu_{max.}$ 1706, 1623, 1593, 1506 cm.$^{-1}$, $[\alpha]_D^{20}$ −31° (*c* 1·32 in ethanol), −19° (*c*, 1·01 in 0·1N-sodium hydroxide), and, after dissolution in 3N-sodium hydroxide (3 min.) and recovery, $[\alpha]_D^{20}$ −21° (*c* 1·01 in ethanol) and −22° (*c* 1·06 in acetone). 7-Chloro-2-hydroxy-4 : 6-dimethoxycoumaran-3-one-2-β-butyric acid, obtained by oxidation of (*d*,*d*)-griseofulvin with zinc permanganate, had $[\alpha]_D^{19}$ −19° (*c* 1·04 in ethanol), unchanged by treatment with cold 3N-sodium hydroxide, and $[\alpha]_D^{22}$ −18·5° (*c* 1·06 in 0·1N-sodium hydroxide). The manganese dioxide, worked up as described previously [2] for the oxidation of (*d*,*d*)-griseofulvin, gave 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid, needles (64 mg.), m. p. 215—218° (decomp.) (from ethyl acetate).

Periodate Oxidation of 7-*Chloro*-2-*hydroxy*-4 : 6-*dimethoxycoumaran*-3-*one*-2-β-*butyric Acid* (IV).—The following improved procedure [3] was used. (*a*) The finely-powdered butyric acid {730 mg.; $[\alpha]_D^{20}$ −19° (*c* 1·1 in ethanol)}, from (*d*,*d*)-griseofulvin, was shaken in water (120 ml.) with 0·09M-sodium periodate (200 ml.) at 23° for 8 days. 3-Chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (420 mg., 85%) was collected and crystallised from ethyl acetate in needles (340 mg.), m. p. and mixed m. p. 219—222° (decomp.). The aqueous filtrate (titration of an aliquot part

showed consumption of 2·06 mol. of periodate) was extracted continuously for 5 days with ether. Recovery gave a gum (480 mg.) which, after sublimation at 80—90°/10^{-3} mm. and crystallisation from benzene, afforded (+)-methylsuccinic acid as needles (340 mg.), m. p. 111—112°, $[\alpha]_D^{22}$ +9·0° (*c* 2·04 in water) (Found: C, 45·7; H, 6·2. Calc. for $C_5H_8O_4$: C, 45·45; H, 6·1%); the anhydride, prepared with a mixture of acetyl chloride and thionyl chloride, crystallised from benzene–light petroleum (b. p. 60—80°) in plates, m. p. 67—69°, $[\alpha]_D^{20}$ +31° (*c* 3·53 in ethanol) (Found: C, 52·8; H, 5·4. Calc. for $C_5H_6O_3$: C, 52·6; H, 5·3%).

(*b*) The butyric acid {330 mg.; $[\alpha]_D^{20}$ −31° (*c* 1·32 in ethanol)}, derived from (*l*,*d*)-griseofulvin, was oxidised as in (*a*) with sodium periodate (2·1 g.) in water (160 ml.), giving (i) 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid (183 mg., 82%), m. p. and mixed m. p. 217—219° (decomp.), and (ii) (+)-methylsuccinic acid (86 mg.), m. p. 111—112°, $[\alpha]_D^{20}$ +8·0° (*c* 1·89 in water) (Found: C, 43·6; H, 6·2%); the anhydride had m. p. 67—69° and $[\alpha]_D^{21}$ +31° (*c* 1·7 in ethanol).

The (+)-methylsuccinic acid and anhydride obtained in (*a*) and (*b*) were identified by direct comparison (mixed m. p. and infrared spectrum) with specimens prepared by resolution of (±)-methylsuccinic acid *via* the strychnine salt.[11]

Reactions of (l,d)(i.e., 2R : 6′R)-7-*Chloro*-4 : 6-*dimethoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione* (II; R = R′ = Me).—(a) *With* 0·5N-*sodium hydroxide*. The (*l*,*d*)-trione (150 mg.) was boiled for 5·5 hr. in nitrogen in 0·5N-sodium hydroxide (25 ml.) which had previously been boiled for 1 hr. in nitrogen. The solid neutral fraction (26 mg.) was collected and adsorbed on alumina (7 × 1 cm.) from a benzene solution (5 ml.). Elution with benzene (150 ml.) and recovery gave 8-chloro-1 : 2 : 3 : 4-tetrahydro-3-oxo-5 : 7-dimethoxy-1-methyldibenzofuran (V) which, after sublimation at <130°/10^{-3} mm., crystallised from methanol in needles (5 mg.), m. p. and mixed m.p. 136—138°, $[\alpha]_D^{18}$ −26° (*c* 0·45 in acetone).

Acidification of the aqueous alkaline filtrate from the reaction mixture afforded a gum which gave no 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid on sublimation.

(b) *With* 0·5N-*sodium methoxide*. The (*l*,*d*)-trione (102 mg.) and sodium (230 mg.) in methanol (20 ml.) were boiled for 5 hr. in nitrogen. Dilution with water, acidification, and removal of methanol *in vacuo* gave a precipitate which was collected; dissolution in sodium carbonate solution (ether washing) and recovery gave unchanged (*l*,*d*)-trione (100 mg.), crystallising from acetic acid in prisms (70 mg.), decomp. 216—218°, identified by its infrared spectrum and optical rotation.

As shown previously,[1] identical treatment of the (*d*,*d*)-trione (1 g.) gave starting material (860 mg.), crystallising from acetic acid in prisms (720 mg.) identified by infrared spectrum, optical rotation, and methylation to (*d*,*d*)-griseofulvin.

(d,d)(i.e., 2S : 6′R)-7-*Chloro*-4 : 6-*diethoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione* (II; R = R′ = Et).—(a) *Preparation*. Treatment of (*d*,*d*)-7-chloro-4 : 6-dimethoxy-6′-methylgrisan-3 : 2′ : 4′-trione (500 mg.) with sodium (550 mg.) in ethanol (50 ml.) as previously described [1] gave the (d,d)-4 : 6-*diethoxy-homologue* (II; R = R′ = Et), crystallising from acetic acid in needles (350 mg.), decomp. 226—228°, $[M]_D^{20}$ +1457° (*c* 1·0 for the sodium salt in water) [Found: C, 58·6; H, 5·1; Cl, 9·7; OEt, 24·2%; equiv. (phenolphthalein), 345. $C_{18}H_{19}O_6Cl$ requires C, 58·9; H, 5·2; Cl, 9·7; 2OEt, 24·5%; *M*, 368], $\nu_{max.}$ 1708, 1650, and 3040 (broad) cm.$^{-1}$.

The neutral fraction of the crude product crystallised from ethanol in needles, m. p. 177—179°, identical (m. p. and mixed m. p.) with (*d*,*d*)-7-chloro-4 : 6 : 4′-triethoxy-6′-methylgris-3′-en-3 : 2′-dione (III; R = R′ = R″ = Et) (see below).

(b) *Ethylation*. The product from the 4 : 6-diethoxy-trione (775 mg.) and excess of diazoethane was chromatographed in benzene (50 ml.) on alumina (30 × 1 cm.), giving: (i) a lower band fluorescing blue. Elution with benzene and recovery yielded (d,d)-7-*chloro*-4 : 6 : 4′-*triethoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione* (III; R = R′ = R″ = Et), needles (350 mg.), m. p. 180—181° (from ethanol) (Found: C, 60·6; H, 5·85; Cl, 9·2; OEt, 33·7. $C_{20}H_{23}O_6Cl$ requires C, 60·8; H, 5·9; Cl, 9·0; 2OEt, 34·2%), $\lambda_{max.}$ ~324, 293, 264, 237 mμ (log ε 3·86, 4·33, 4·35, 4·4), $\nu_{max.}$ 1704 and 1655 cm.$^{-1}$; and (ii) an upper band fluorescing blue. Elution with benzene–methanol (99 : 1) gave the isomeric (d,d)-7-*chloro*-4 : 6 : 2′-*triethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (I; R = R′ = R″ = Et) which crystallised from benzene–light petroleum (b. p. 60—80°) in needles (240 mg.), m. p. 173—175°, $[\alpha]_D^{20}$ +297° (*c* 0·85 in acetone) (Found: C, 60·7; H, 6·0; Cl, 8·9%), $\lambda_{max.}$ ~323, 292·5, ~256, 237 mμ (log ε 3·79, 4·38, 4·19, 4·33), $\nu_{max.}$ 1696 and 1657 cm.$^{-1}$.

[11] Ladenberg, *Ber.*, 1895, **28**, 1170.

Oxidation of the latter compound (97 mg.) in acetic acid (1·5 ml.) with chromium trioxide (300 mg.) in acetic acid (1·5 ml.) and water (0·6 ml.) as described [1] for 7-chloro-2′-ethoxy-4 : 6-dimethoxy-6′-methygris-2′-en-3 : 4′-dione (I; R = Et, R′ = R″ = Me) gave 3-ethoxy-2 : 5-toluquinone (1 mg.), m. p. and mixed m. p. 54—56°.

Each of the isomeric ethyl ethers with boiling 2N-hydrochloric acid in ethanol, as for the acid hydrolysis of griseofulvin,[8] gave the parent trione, identified by infrared spectrum and elementary analysis.

(c) *Methylation.* The product from the 4 : 6-triethoxy-trione (775 mg.) and excess of diazomethane was chromatographed on alumina (21 × 1·5 cm.), giving: (i) a lower band fluorescing blue; elution with benzene yielded (d,d)-7-*chloro*-4 : 6-*diethoxy*-4′-*methoxy*-6′-*methylgris*-3′-*en*-3 : 2′-*dione* (III; R = Me, R′ = R″ = Et), needles, m. p. 218—219° (from methanol) (Found: C, 59·6; H, 5·6; Cl, 9·4. $C_{19}H_{21}O_6Cl$ requires C, 59·9; H, 5·5; Cl, 9·3%), $\lambda_{max.}$ 320, 292, 263, 235 mμ (log ε 3·76, 4·27, 4·27, 4·31), $\nu_{max.}$ 1704 and 1662 cm.$^{-1}$; and (ii) an upper band fluorescing blue; elution with benzene–methanol (99 : 1) gave the isomeric (d,d)-7-*chloro*-4 : 6-*diethoxy*-2′-*methoxy*-6′-*methylgris*-2′-*en*-3 : 4-*dione* (I; R = Me, R′ = R″ = Et), crystallising from ethanol in prisms, m. p. 208—212° (Found: C, 59·7; H, 5·8; Cl, 9·3%), $\lambda_{max.}$ ~325, 292, 255, 233 mμ (log ε 3·87, 4·46, 4·29, 4·48), $\nu_{max.}$ 1707 and 1673 cm.$^{-1}$.

(d) *Oxidation.* The 4 : 6-diethoxy-trione (200 mg.) in acetone (50 ml.) was treated with powdered potassium permanganate (800 mg.). After 16 hr. at room temperature, the precipitated manganese salts were collected and extracted with dilute aqueous ammonia; acidification gave 3-*chloro*-4 : 6-*diethoxy*-2-*hydroxybenzoic acid* (VI; R = R′ = Et), crystallising from ethyl acetate in needles (12 mg.), m. p. 171°(decomp.) (Found: C, 51·0; H, 5·1; Cl, 14·0. $C_{11}H_{13}O_5Cl$ requires C, 50·7; H, 5·0; Cl, 13·6%), $\nu_{max.}$ 1660 and 3200 cm.$^{-1}$.

The ethyl ether ethyl ester, prepared with diazoethane, crystallised from light petroleum (b. p. 40—60°) in plates, m. p. 65—67°, identical (mixed m. p. and infrared spectrum) with the synthetic specimen described below.

Ethyl 3-*Chloro*-2 : 4 : 6-*triethoxybenzoate*.—*Ethyl* 2 : 4 : 6-*triethoxybenzoate*, obtained from 2 : 4 : 6-trihydroxybenzoic acid (2·0 g.) and diazoethane, crystallised from light petroleum (b. p. 40—60°) in plates (1·8 g.), m. p. 88—89° (Found: C, 64·1; H, 8·1; OEt, 60·5. $C_{15}H_{22}O_5$ requires C, 63·8; H, 7·85; 4OEt, 63·7%). This ester (286 mg.) in carbon tetrachloride (15 ml.) was treated slowly with chlorine (78 mg.) in carbon tetrachloride (6·3 ml.). After 12 hr. at room temperature the mixture was washed with water, dried, and evaporated, giving *ethyl* 3-*chloro*-2 : 4 : 6-*triethoxybenzoate*, needles (200 mg.), m. p. 67—68° [from light petroleum (b. p. 40—60°)] (Found: C, 57·1; H, 6·8; Cl, 11·6. $C_{15}H_{21}O_5Cl$ requires C, 56·9; H, 6·7; Cl, 11·2%).

(d,d)(i.e., 2S : 6′R)-7-*Chloro*-6-*ethoxy*-4-*methoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione* (II; R = Me, R′ = Et).—7-Chloro-6 : 2′-diethoxy-4-methoxy-6′-methylgris-2′-en-3 : 4′-dione [9] (45 mg.) in ethanol (5 ml.) and 2N-hydrochloric acid (5 ml.) was hydrolysed as for griseofulvin,[8] giving (d,d)-7-*chloro*-6-*ethoxy*-4-*methoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione*, stout needles, decomp. 234—236° (Found: C, 57·9; H, 5·1; Cl, 10·0. $C_{17}H_{17}O_6Cl$ requires C, 57·9; H, 4·85; Cl, 10·1%). The infrared spectrum (bands at 1708, 1651, and ~3125 cm.$^{-1}$) was very similar to, but distinct from, that of 7-chloro-4 : 6-diethoxy-6′-methylgrisan-2 : 2′ : 4′-trione (see above).

Action of 0·04N-*Sodium Ethoxide on* (d,d)-*Griseofulvin*.—Griseofulvin (2·0 g.) was heated under reflux for 5 hr. with sodium (0·8 g.) in ethanol (800 ml.). After dilution with water (400 ml.) and acidification, the ethanol was removed *in vacuo*, giving a gum (A; 1·2 g.) which was collected after 18 hr. at 0°. After storage at 0° for several days, a second fraction (B; 200 mg.) was collected.

A solution of fraction (A) in ether was extracted with sodium carbonate solution, and the recovered neutral fraction in benzene (15 ml.) was chromatographed on alumina (20 × 1·5 cm.), giving: (*a*) a narrow band fluorescing blue; elution with benzene gave an oil (5 mg.) which was discarded; (*b*) a broad band fluorescing blue; elution with benzene gave a solid (35 mg.), crystallising from ethanol in needles, m. p. 174—178°, identical (mixed m. p. and infrared spectrum) with (*d,d*)-7-chloro-4 : 6 : 4′-triethoxy-6′-methylgris-3′-en-3 : 2′-dione (III; R = R′ = R″ = Et); and (*c*) upper broad band fluorescing blue; elution with benzene–methanol (99 : 1) gave a gum (400 mg.) which yielded a solid (130 mg.), m. p. 175—200°, on treatment with ethanol. This solid from fraction (*c*), combined with a similar fraction (20 mg.), m. p. 170—190°, from (*b*), was washed with ether and crystallised from ethanol to constant m. p. (210—212°), giving prisms of the (?) mixture of (*d,d*)- and (*l,d*)-7-chloro-6 : 2′-diethoxy-6′-methylgris-2′-en-3 : 4′-dione (I; R = R″ = Et, R′ = Me), $[M]_D^{20}$ +308° (*c* 0·82 in acetone)

(Found: C, 59·3, 59·3; H, 5·8, 5·9, 5·9; Cl, 9·2. Calc. for $C_{19}H_{21}O_6Cl$: C, 59·9; H, 5·6; Cl, 9·3. Calc. for $C_{20}H_{23}O_6Cl$: C, 60·8; H, 5·9; Cl, 9·0%); analysis of the alkyl iodide, obtained by the Zeisel method, by gas chromatography as described by Haslam, Hamilton, and Jeffs,[12] indicated the presence of methoxyl and ethoxyl in the approximate ratio of 1 : 1·6. The ultraviolet absorption spectra, as described by Grove *et al.*[3], of this solid showed $\nu_{max.}$ 1718 and 1667 cm.$^{-1}$.

The ether-soluble fraction of the solid, m. p. 175—200°, obtained from band (*c*) was chromatographed in ether on alumina, giving two bands fluorescing blue: (i) A lower band eluted with ether gave an unidentified solid which, after repeated crystallisation from methanol, was obtained as needles (2 mg.), m. p. 200°, $\lambda_{max.}$ ~325, 291, 263, 233 ($E^{1\%}_{1\,cm.}$ 153, 444, 566, 578), $\nu_{max.}$ 1700 and 1653 cm.$^{-1}$: this compound was distinct (mixed m. p.) from (*d,d*)- and (*l,d*)-7-chloro-4 : 6 : 4′-trimethoxy-6′-methylgris-3′-en-3 : 2′-dione (III; R = R′ = R″ = Me) and the (*d,d*)-4′-ethoxy-homologue (III; R = Et, R′ = R″ = Me) and from the 2′-ethoxy-homologue of (*d,d*)-griseofulvin. (ii) An upper band, elution of which with ether–methanol (99 : 1) yielded a little more of the (?) mixture of (*d,d*)- and (*l,d*)-diastereoisomers of the homologue (I; R = R″ = Et, R′ = Me).

The acidic gum (600 mg.), recovered from the sodium carbonate extract of fractions A and B, was treated with excess of diazoethane and then chromatographed on alumina (30 × 2 cm.) in ether. A narrow band fluorescing blue, eluted with ether and discarded, was followed by a broad band fluorescing blue which was fractionally eluted as follows: (*x*) ether (50 ml.) eluted (*d,d*)-7-chloro-4 : 6 : 4′-triethoxy-6′-methylgris-3′-en-3 : 2′-dione (III; R = R′ = R″ = Et), needles (30 mg.), m. p. and mixed m. p. 177—180°; (*y*) ether (3 × 100 ml.) eluted gums (267 mg.); and (*z*) ether–ethanol (99 : 1) (100 ml.) eluted an unidentified compound, crystallising from ethanol in needles, m. p. 173—175°, $\lambda_{max.}$ ~323, 290, ~252, 236 ($E^{1\%}_{1\,cm.}$ 146, 579, 359, 589), $\nu_{max.}$ 1716 and 1665 cm.$^{-1}$. This compound depressed the m. p.s of the 6 : 2′-diethoxy- and the 4 : 6 : 2′-triethoxy-homologue of (*d,d*)-griseofulvin.

The author is indebted to Mr. P. J. Suter and Mr. J. Ingle for their invaluable assistance in the chromatographic separation of the diastereoisomers, and to Dr. J. Haslam, Imperial Chemical Industries Limited, Plastics Division, Welwyn Garden City, for the ethoxyl–methoxyl determination.

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The Frythe, Welwyn, Herts. [*Received, December 29th*, 1958.]

[12] Haslam, Hamilton, and Jeffs, *Analyst*, 1958, **83**, 66.

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362. *Griseofulvin. Part XV.*[1] *Some Derivatives of the* (l,d)-*Stereoisomer of Griseofulvin.*

By A. W. Dawkins and T. P. C. Mulholland.

(*l,d*)-7-Chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3 : 4′-dione (I) has been degraded to (*l,d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (X) and (*l,d*)-7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one (IX).

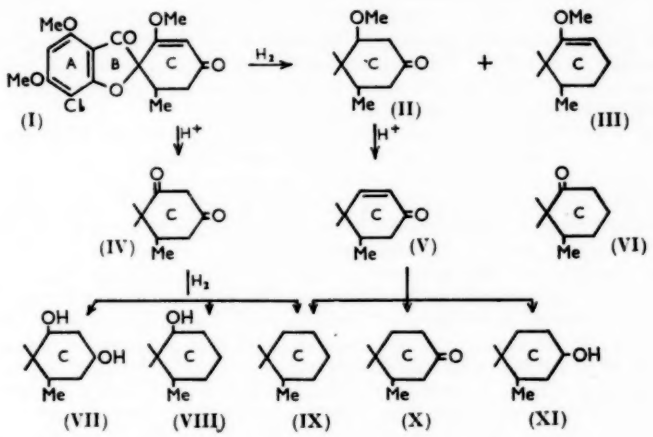
It has been shown [1] that griseofulvin (I) can be converted into a diastereoisomer in which the configuration at the spiran centre of asymmetry is inverted. According to the convention of Cahn *et al.*[2] griseofulvin and the above diastereoisomer were assigned the configurations (2*S* : 6′*R*) and (2*R* : 6′*R*) respectively, but for reasons stated previously [1] the configurations of these compounds are denoted in this and later papers by (*d,d*) and (*l,d*) respectively, the spiran centre being the first mentioned. (Configurations according to the convention of Cahn *et al.* are given in the Experimental part.)

For comparison with synthetic racemates, described in subsequent papers, the (*l,d*)-stereoisomers of 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3 : 4′-dione (X) and 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one (IX) were required.

[1] Part XIV, MacMillan, preceding paper.
[2] Cahn, Ingold, and Prelog, *Experientia*, 1956, **12**, 81.

The former was prepared from the (*l*,*d*)-diastereoisomer (I) by Mulholland's method.[3,4] Hydrogenation in the presence of palladium–carbon gave a mixture of the (*l*,*d*)-dihydro-derivative (II) and (*l*,*d*)-7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgris-2′-en-3-one (III).

Unlike the (*d*,*d*)-isomer,[4] the (*l*,*d*)-compound (III) was not converted into the corresponding ketone (VI) by 80% acetic acid. Similar treatment [5] of the (*l*,*d*)-ether (II) gave



dimorphic (*l*,*d*)-7-chloro-4 : 6-dimethoxy-6′-methylgris-2′-en-3 : 4′-dione (V) which on hydrogenation on palladium–carbon gave the required (*l*,*d*)-ketone (X) as the only isolable product.

Reduction of the (*l*,*d*)-dione (V) in the presence of Raney nickel gave the (*l*,*d*)-isomers of the ketone (X), the alcohol (XI), and 7-chloro-4 : 6-dimethoxy-2′-methylgrisan-3-one (IX). Reduction with Adams catalyst gave (*l*,*d*)-monoketone (IX) and -diketone (X) and an intractable alcoholic fraction. Previously, the (*d*,*d*)-monoketone (IX) had been obtained by hydrogenation of the (*d*,*d*)-trione (IV) with Adams catalyst. When a commercial Adams catalyst was used reduction of the (*l*,*d*)-trione (IV) gave the (*l*,*d*)-isomers of the diol (VII) and alcohol (VIII) but no monoketone (IX). With a catalyst prepared by Adams's method [7] the (*l*,*d*)-monoketone was obtained but only in traces.

Attempts to find a better method of preparation of the (*l*,*d*)-monoketone (IX), by using as models the available (*d*,*d*)-ketones (V) and (X) failed. Wolff–Kishner reduction of the diketone (X) gave no crystalline products; and although the trimethylene dithioketals of (V) and (X) were obtained, fission did not take place on treatment with nickel (cf. ref. 9). The alcohol obtained by hydrogenation of the (*l*,*d*)-trione (IV) differed from the isomeric (*l*,*d*)-alcohol (XI) whose structure is shown by its formation from the (*l*,*d*)-dione (V); hence it is assigned the structure (*l*,*d*-VIII), analogous to the (*d*,*d*)-stereoisomer obtained [6] from the (*d*,*d*)-trione (IV). Unlike the (*d*,*d*)-stereoisomer, the (*l*,*d*)-alcohol (VIII) could not be oxidised to the corresponding ketone with chromic acid.

The infrared spectra of the (*l*,*d*)-ketones (IX) and (X) in solution were distinct from those of their (*d*,*d*)-stereoisomers, and the m. p.s of mixtures of (*l*,*d*)- and (*d*,*d*)-forms were depressed. The relation between these compounds and synthetic racemates will be discussed later.

[3] Mulholland, *J.*, 1952, 3987.
[4] *Idem*, *J.*, 1952, 3994.
[5] Riley, personal communication.
[6] Grove, MacMillan, Mulholland, and Rogers, *J.*, 1952, 3949.
[7] *Org. Synth.*, Coll. Vol. I, 1941, p. 463.

Experimental

M. p.s are corrected. Microanalyses are by Messrs. W. Brown and A. G. Olney. Absorption spectra (in ethanol) and alumina for chromatography were obtained as described previously.[8] Unless otherwise stated, infrared spectra were determined for Nujol " mulls."

Hydrogenation of the (l,d)(i.e., 2R : 6′R)-*Diastereoisomer* (I).—The compound (352 mg.) in ethyl acetate (30 ml.) was shaken in hydrogen at room temperature and pressure in the presence of a catalyst prepared by heating palladium chloride (300 mg.) and water (20 ml.) to the b. p., cooling the mixture, and adding charcoal (1·20 g.). Absorption (1·7 mol.) almost ceased after 7 min. Recovery of the product gave a gum (350 mg.) which was chromatographed in benzene (5 ml.) on alumina (20 × 2 cm.). Fluorescent bands were eluted in ultraviolet light: (i) Ether–light petroleum (b. p. 40—60°; 1 : 1) eluted a violet band, giving a solid (158 mg.). (ii) Ether–methanol (100 : 1) eluted a blue band, giving a solid (183 mg.).

Fraction (i) crystallised from benzene–light petroleum (b. p. 60—80°) in prisms, m. p. 183—184° of (l,d)(i.e., 2R : 6′R)-7-*chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgris*-2′-*en*-3-*one* (III), $[\alpha]_D^{23}$ +39° ± 3° (*c* 0·75 in acetone) (Found: C, 60·4; H, 5·7; OMe, 25·6. $C_{17}H_{19}O_5Cl$ requires C, 60·3; H, 5·65; 3OMe, 27·5%), $\nu_{max.}$ 1709 (C=O) and 1675 cm.$^{-1}$ (weak, C=C). The compound did not react with Brady's reagent. Hydrolysis with 80% acetic acid [4] failed to yield a diketone (VI).

Fraction (ii) crystallised from acetone–light petroleum in prisms of (l,d)(i.e., 2R : 6′R)-7-*chloro*-4 : 6 : 2′-*trimethoxy*-6′-*methylgrisan*-3 : 4′-*dione* (II) which melted (loss of solvent) at *ca.* 100°, resolidified and remelted at 180—182°, $[\alpha]_D^{18}$ 0° ± 3° (*c* 0·68 in acetone) (Found, for a sample dried at 100°: C, 57·6; H, 5·5; OMe, 24·9. $C_{17}H_{19}O_6Cl$ requires C, 57·5; H, 5·4; 3OMe, 26·2%), $\nu_{max.}$ 1703, 1712 cm.$^{-1}$. The compound gave a precipitate with Brady's reagent.

(l,d)(i.e., 2S : 6′R)-7-*Chloro*-4 : 6-*dimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (V).—A solution of (*l,d*)-7-chloro-4 : 6 : 2′-trimethoxy-6′-methylgrisan-3 : 4′-dione (II) (1·409 g.) in 80% acetic acid (140 ml.) was heated under reflux for 15 hr. and evaporated to dryness *in vacuo*. Crystallisation of the residue from methanol gave needles, (i) m. p. 195—196° (632 mg.) and (ii) m. p. 188—192° (155 mg.), and a residue. Re-treatment of the residue with 80% acetic acid for 6 hr. and recovery gave a further crop of m. p. 189—194° (69 mg.). Crystallisation of the combined products from methanol and dilute methanol gave the (l,d)-*dione* (V) as needles, m. p. 196—198°. In the first two experiments the product had m. p. 166—167°, converted into the form of higher m. p. on melting and cooling or by seeded crystallisation. A mixture of the two forms had m. p. 196—198°, $[\alpha]_D^{21}$ −148° ± 3° (*c* 1·15 in acetone) (Found: C, 59·8; H, 4·7; OMe, 18·5. $C_{16}H_{15}O_5Cl$ requires C, 59·5; H, 4·7; 2OMe, 19·2%), $\nu_{max.}$ 1708, 1685 cm.$^{-1}$ (low m. p.), or 1700, 1689 cm.$^{-1}$ (high m. p.). The compound was unsaturated to neutral permanganate and gave a precipitate with Brady's reagent.

Hydrogenation of (l,d)(i.e., 2S : 6′R)-7-*Chloro*-4 : 6-*dimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (V).—(i) *With a palladium catalyst.* A solution of the compound (495 mg.) in ethyl acetate (50 ml.) was shaken in hydrogen at room temperature and pressure in the presence of a catalyst prepared from palladium chloride (500 mg.), water (30 ml.), and charcoal (2·00 g.) as described above. Absorption (1·0 mol.) was complete in 1 min. The crude recovered product was chromatographed in benzene (50 ml.) on alumina (12 × 4 cm.) and a narrow blue-fluorescent band was eluted in ultraviolet light with benzene–methanol (100 : 1). The recovered gum (451 mg.) was twice sublimed at 10^{-4} mm. (bath, 120—140°), and the sublimate (374 mg.) crystallised from methanol in prisms, m. p. 168—170° of (l,d)(i.e., 2S : 2′R)-7-*chloro*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3 : 4′-*dione* (X), $[\alpha]_D^{22}$ −30° ± 3° (*c* 1·34 in acetone) (Found: C, 59·2; H, 5·4. $C_{16}H_{17}O_5Cl$ requires C, 59·2; H, 5·3%). The infrared spectra in Nujol (C=O, 1709 cm.$^{-1}$; OH absent) and in chloroform (C=O, 1702 cm.$^{-1}$ broad) were distinct from the corresponding spectra of the (*d,d*)-isomer,[3] and the m. p. of a mixture was depressed. The compound was saturated to neutral permanganate and gave a precipitate with Brady's reagent.

(ii) *With platinum oxide.* The compound (150 mg.) and platinum oxide (100 mg.) prepared by the Adams method [7] in methanol (30 ml.) were shaken with hydrogen at room temperature and pressure until absorption nearly stopped (3·1 mol. in 40 min.). The recovered gum was chromatographed in benzene on alumina (17 × 2·3 cm.). Elution in ultraviolet light removed fluorescent bands: (i) Ether eluted a violet band, giving a solid (8 mg.), m. p. 128—144°. (ii) Ether–methanol (100 : 1) removed a blue band, giving a gum (118 mg.). (iii) Ether–methanol (100 : 3) eluted a blue band, giving a gum (11 mg.).

[8] Mulholland and Ward, *J.*, 1954, 4676.

Fraction (i) crystallised from ether–light petroleum (b. p. 40—60°) in prisms, m. p. 149—153°, of (l,d)(i.e., 2S : 2′R)-7-*chloro*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3-*one* (IX) identical (mixed m. p. and infrared spectrum) with material obtained by another method (see below), $[\alpha]_D^{20}$ −24° ± 3° (*c* 0·55 in acetone) (Found: C, 61·7; H, 6·1. $C_{16}H_{19}O_4Cl$ requires C, 61·8; H, 6·1%). The infrared spectrum was distinct from that of the (*d*,*d*)-isomer obtained [6] from griseofulvin and the m. p. of a mixture was depressed.

Fraction (ii) was sublimed *in vacuo* and crystallised from methanol and dilute methanol, giving the (*l*,*d*)-dione (X) as prisms (43 mg.), m. p. and mixed m. p. 168—170°.

Fraction (iii) contained alcoholic hydroxyl (infrared spectrum) but was intractable.

(iii) *With Raney nickel.* The compound (105 mg.) in ethanol (10 ml.) was shaken with hydrogen at room temperature and pressure in the presence of Raney nickel (*ca.* 0·5 g.) until 2 mol. were absorbed (5 min.). Chromatography of the recovered gum in benzene on alumina (24 × 1·2 cm.) and elution of fluorescent bands in ultraviolet light with ether–methanol (100 : 3) gave gums on recovery: (i) a violet band (16 mg.); (ii) a blue band (31 mg.); (iii) a blue band (17 mg.).

Fraction (i) was sublimed at 120—130°/10^{-4} mm. and chromatographed on alumina (20 × 0·5 cm.) in ether. Elution with ether removed a small blue fluorescent band, then a larger blue band. Recovery from the latter gave a gum (4 mg.) which crystallised from methanol, giving needles (0·6 mg.), m. p. 120—137°, raised to 140—146° by further recrystallisation and not depressed on admixture with the (*l*,*d*)-ketone (IX) (see above).

Fraction (ii) crystallised from methanol and dilute methanol in prisms (9 mg.) of the (*l*,*d*)-dione (X), m. p. and mixed m. p. 165—168°.

Fraction (iii) gave a solid (18 mg.) on trituration with ether. Recrystallisation from dilute methanol (needles) and from ethyl acetate–light petroleum (b. p. 60—80°) gave prisms of (l,d)(i.e., 2S : 2′R)-7-*chloro*-4′-*hydroxy*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3-*one* (XI), m. p. 193—195° (Found: C, 59·3; H, 6·1. $C_{16}H_{19}O_5Cl$ requires C, 58·8; H, 5·9%), $\nu_{max.}$ 1697 (C=O), 3520 (OH) cm.$^{-1}$, $\lambda_{max.}$ at 236, 286, 320 mμ (log ε 4·20, 4·32, 3·71 respectively). The compound did not react with Brady's reagent, and the m. p. was depressed on admixture with the isomeric (*l*,*d*)-alcohol (VIII) (see below).

(l,d)(i.e., 2R : 6′R)-7-*Chloro*-4 : 6-*dimethoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione* (IV).—A mixture of the (*l*,*d*)-diastereoisomer (I) (2·60 g.), ethanol (500 ml.), and 2N-hydrochloric acid (625 ml.) was heated under reflux for 5 hr. Most of the ethanol was evaporated *in vacuo*. The residual solution at 0° afforded a solid in 18 hr. This was dissolved in sodium hydrogen carbonate solution, and the solution was washed with ether and acidified with hydrochloric acid, giving the (*l*,*d*)-trione (IV) (1·65 g.), m. p. 215—216°, $[\alpha]_D^{20}$ +112° (*c* 1·07 for the sodium salt in water). It was identical (infrared spectrum) with material obtained by MacMillan [1] by fractionation of a mixture of the (*l*,*d*)- and the (*d*,*d*)-trione.

Hydrogenation of (l,d)(i.e., 2R : 6′R)-7-*Chloro*-4 : 6-*dimethoxy*-6′-*methylgrisan*-3 : 2′ : 4′-*trione* (IV).—The trione (1·00 g.) in acetic acid (150 ml.) was hydrogenated at room temperature and pressure in the presence of a platinum oxide catalyst prepared by the Adams method.[7] Absorption (3 mol.) was complete in 6 hr. The recovered product was chromatographed on alumina (20 × 1·0 cm.), and fluorescent bands were collected in ultraviolet light, giving gums on recovery: (i) benzene, a pale blue band (10 mg.); (ii) benzene–methanol (100 : 1), a bright blue band (520 mg.); (iii) benzene–methanol (25 : 1), a violet band (316 mg.).

Fraction (i) was combined with the forerun (*a*) from rechromatography of fraction (ii) (see below) and purified by sublimation, chromatography, and crystallisation from methanol and ethanol, giving prisms (2 mg.), m. p. 153—155°, identified by the infrared spectrum and mixed m. p. as the (*l*,*d*)-monoketone (IX) (see above).

Fraction (ii) was chromatographed on alumina (15 × 1·0 cm.) in benzene and eluted with the same solvent, giving (*a*) a blue fluorescent forerun and (*b*) a broad light blue band. On recovery, band (*b*) gave a glass which was purified by sublimation followed by crystallisation from ethyl acetate–light petroleum (b. p. 40—60°) and from dilute methanol, giving prisms (230 mg.), m. p. 189—190°, of (l,d)(i.e., 2R : 6′R)-7-*chloro*-2′-*hydroxy*-4 : 6-*dimethoxy*-6′-*methylgrisan*-3-*one* (VIII), $[\alpha]_D^{22}$ −27° ±3° (*c* 0·45 in acetone) (Found: C, 58·95; H, 5·9. $C_{16}H_{19}O_5Cl$ requires C, 58·8; H, 5·8%), $\nu_{max.}$ 1695 (C=O), 3490 (OH) cm.$^{-1}$. The compound was saturated to neutral permanganate and did not react with Brady's reagent. The m. p. was depressed on admixture with the isomeric (*l*,*d*)-alcohol (XI) (see above). Attempts to oxidise the alcohol to the (*l*,*d*)-ketone (VI) with chromic acid as described [6] for the (*d*,*d*)-isomer failed. At 30° no

oxidation occurred; at 60—100° the only isolable product was 3-chloro-2-hydroxy-4 : 6-dimethoxybenzoic acid.

Fraction (iii) was dissolved in water (300 ml.) by shaking at room temperature for 24 hr. The filtered solution was concentrated to *ca.* 30 ml. and cooled to 5—10°, giving prisms (280 mg.). Recrystallisation from ethyl acetate gave (l,d)(i.e., 2R : 6′R)-7-*chloro*-2′ : 4′-*dihydroxy*-4 : 6-*dimethoxy*-6′-*methylgrisan*-3-*one* (VII) as needles, m. p. 213—215°, $[\alpha]_D^{19}$ +43° ± 3° (*c* 0·50 in acetone) (Found: C, 56·4; H, 5·7. $C_{16}H_{19}O_6Cl$ requires C, 56·1; H, 5·55%), $\nu_{max.}$ 1695 (C=O) 3475, 3430, 3220 (OH) cm.$^{-1}$.

Attempted Reduction of (d,d)(i.e., 2R : 2′R)-7-*Chloro*-4 : 6-*dimethoxy*-2′-*methylgrisan*-3 : 4′-*dione* (X).—A current of dry hydrogen chloride was passed through a mixture of the compound (325 mg.) and propane-1 : 3-dithiol (119 mg.) in chloroform (5 ml.) for 2 hr. at 0°. The solution was diluted with chloroform, washed with sodium hydroxide and water, dried, and evaporated, giving a glass (383 mg.). The solid (357 mg.; m. p. 210—212°) obtained by heating the glass with light petroleum (b. p. 40—60°) crystallised from methanol in prisms, m. p. 211—212° of (d,d)(i.e., 2R : 2′R)-7-*chloro*-4 : 6-*dimethoxy*-2′-*methyl*-3-*oxogrisan*-4′-*one trimethylene dithioketal* (Found: C, 54·8; H, 5·7; Cl, 8·5; S, 14·8; OMe, 14·4. $C_{19}H_{23}O_4S_2Cl$ requires C, 55·0; H, 5·6; Cl, 8·5; S, 15·5; 2OMe, 14·9%), $\nu_{max.}$ 1696 cm.$^{-1}$ (C=O).

Attempted fission of the ketal failed. An ethanolic solution containing a ten-fold excess of freshly prepared W6 Raney nickel was shaken for 2 hr. at room temperature, heated under reflux for 40 hr., and finally shaken in hydrogen for 48 hr., but in each case only starting material was recovered.

Attempted Reduction of (d,d)(i.e., 2R : 6′R)-7-*Chloro*-4 : 6-*dimethoxy*-6′-*methylgris*-2′-*en*-3 : 4′-*dione* (V).—Treatment of the above compound with propane-1 : 3-dithiol as described for the (*d*,*d*)-diketone (X) gave an intractable, unsaturated, sulphur-containing glass, insoluble in organic solvents, which was recovered (infrared spectrum) from attempts to split it by the above methods.

The authors are indebted to Dr. L. A. Duncanson for the infrared spectra and to Messrs. H. J. Clase, M. C. Gilbert, and J. H. E. Marsden for technical assistance.

AKERS RESEARCH LABORATORIES, IMPERIAL CHEMICAL INDUSTRIES LIMITED,
THE FRYTHE, WELWYN, HERTS. [*Received, January 5th*, 1959.]

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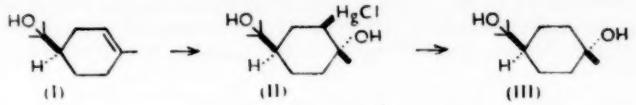
363 *Aspects of Stereochemistry. Part XIII.*[1] *The Reaction of (+)-Carvomenthene with Mercuric Acetate in Water.*

By H. B. HENBEST and R. S. MCELHINNEY.

In the reaction of 1-methyl*cyclo*hexenes with mercuric acetate in water, replacement of a 4-(1-hydroxy-1-methylethyl) substituent (in α-terpineol) by a 4-*iso*propyl substituent (in carvomethene) causes a reversal of the direction of perpendicular addition of HgX and OH groups. Mechanisms for the two reactions are discussed. Pure (+)-carvomenthene has been prepared from its hydroxy-chloromercuri-adduct, and the *cis*- and *trans*-isomers of β-terpineol and *p*-menthan-1-ol have been further characterised.

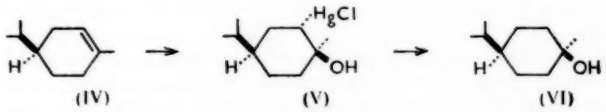
IN a previous paper[1] on the reactions of unsymmetrical olefinic bonds with mercuric acetate in water or in methanol, it was shown that several *cyclo*hexenes containing a Lewis-base substituent at the 4-position each yielded a single adduct, in which the new anionic substituent (OH or OMe) was placed in a *trans*-1 : 4-relation to the original Lewis-base substituent. It was also pointed out that the reaction of α-terpineol (I; absolute configuration) apparently proceeds by the same mechanism (involving retention of the mercuri-group on the same side of the molecule as the Lewis-base group), as the resulting adduct (II) gives *cis*-terpin (III; discussion of stereochemistry below) on reductive removal of the

[1] Part XII, Henbest and Nicholls, *J.*, 1959, 227.



(I) (II) (III)

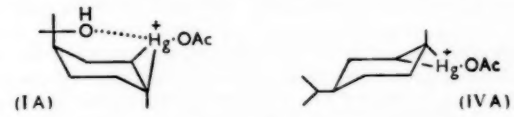
mercurial group. In order to determine the importance of the hydroxyl group in the side-chain of α-terpineol in directing the formation of the adduct (II), we have now examined the reaction of its deoxy-analogue, (+)-carvomenthene (IV; absolute configuration), with mercuric acetate in water.



(IV) (V) (VI)

This reaction gave a single crystalline mercurial in at least 74% yield, after the acetoxymercuri-group in the initial reaction product had been converted into a chloromercuri-group by treatment with sodium chloride. The structure (V) for this adduct was established by its reduction with hydrazine [2] to *trans-p*-menthanol (VI; discussion of stereochemistry below). Carvomenthene was also formed in the reduction of the mercurial with hydrazine, and the olefin was obtained as the only product when sodium–ethanol was used as the reducing agent; in either case the elimination of the chloromercuri- and hydroxy-groups may be helped by their diaxial arrangement when the molecule is in the conformation with the *iso*propyl group equatorial.

The reactions of α-terpineol (I) and carvomenthene (IV) with mercuric acetate in water differ, therefore, in the direction of attachment of the entering hydroxyl group, and hence in the direction of initial addition of the mercury electrophile. In the case of carvomenthene, the direction of addition conforms to the Markownikow rule and to the rule of diaxial addition to *cyclo*hexenes, on the assumption that the molecule undergoes reaction in the conformation where the *iso*propyl group is equatorial (cf. mercurinium ion, IVA). The fact that the initial attack of the mercury electrophile is towards the less hindered side of the molecule (*trans* to the *iso*propyl group) may be an additional factor in causing the formation of the adduct (V). In α-terpineol, the hydroxyl group on the



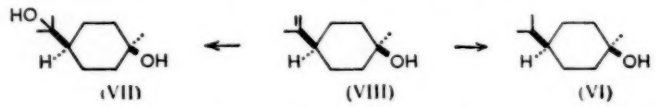
(IA) (IVA)

*iso*propyl side-chain can act as a Lewis base (cf. mercurinium ion, IA) to hold the mercury electrophile on to that side of the molecule,[1] and the direction of perpendicular addition of the HgX and OH groups is reversed.

The β-*Terpineols and* p-*Menthanols.*—The geometrical configurations of each of these pairs of compounds were uncertain until Pascual and Coll [3] established the structure of the " terpins." The lower-melting terpin, which forms a hydrate, has the structure (VII). It was called " *cis*-terpin " but, as Barnes [4] has pointed out, *trans*-terpin is a better name as it indicates the *trans*-arrangement of the alkyl groups. The isomeric higher-melting terpin, which does not form a hydrate, is best named *cis*-terpin (cf. III). In 1902, Stephan and Helle [5] isolated a " β-terpineol," m. p. 32—33°, from a commercial terpineol mixture.

[2] Wright, *Canad. J. Chem.*, 1950, **30**, 268.
[3] Pascual and Coll, *Anal. real soc. espan. Fis. Quim.*, 1953, **49**, 547, 553.
[4] Barnes, *Austral. J. Chem.*, 1958, **11**, 134.
[5] Stephan and Helle, *Ber.*, 1902, **35**, 2148.

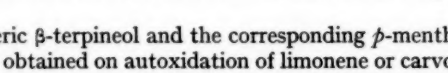
The fact that *trans*-terpin (VII) can be readily obtained [6] from this β-terpineol shows that the latter compound has the structure (VIII). The *p*-menthanol, obtained [7] by hydrogenation of β-terpineol, must therefore be the *trans*-compound (VI).[4] Repetition of this



(VII) (VIII) (VI)

hydrogenation gave *trans*-*p*-menthanol (VI) identical with the product obtained (above) by reduction of the mercurial from carvomenthene—hence the assignment of structure (II) to the mercurial.

Recently, an isomeric β-terpineol and the corresponding *p*-menthanol have been separated from the mixture obtained on autoxidation of limonene or carvomenthene followed by partial or complete reduction.[8] By exclusion, the new isomers must be the *cis*-compounds (IX and X). In these new isomers, the conformations with equatorial hydroxyl and *iso*propenyl (or *iso*propyl) groups should predominate, whereas the hydroxyl groups in the corresponding old isomers (VIII and VI) will tend to be axial. In agreement, the new



(IX) (X)

isomers have the higher boiling points and are also more slowly eluted on vapour-phase chromatography. All four tertiary alcohols give crystalline phenylurethanes, and they can also be differentiated by differences in their absorption in the 900—1200 cm.$^{-1}$ region of the infrared spectrum.

Experimental

M. p.s were determined on a Kofler hot stage. Optical rotations were determined by using dilute (1—2%) solutions in " AnalaR " benzene.

Purification of (+)-*Carvomenthene* (IV).—(+)-Limonene (27·2 g.) in ethanol (100 c.c.) was shaken with hydrogen at atmospheric pressure in the presence of pre-reduced Adams catalyst (0·272 g.). When one mol. had been absorbed (70 min.), the hydrocarbon was isolated with pentane. The crude carvomenthene (24·5 g.) had b. p. 52—53°/8 mm., n_D^{25} 1·4530, $[\alpha]_D$ +91°; it was used to prepare the mercurial (see below). A mixture of the pure mercurial (18·5 g.), 2N-sulphuric acid (200 c.c.), and light petroleum (b. p. 40—60°; 100 c.c.) was stirred vigorously at 20° for 6 hr. Filtration removed a yellow solid (3·6 g.), and then the carvomenthene was isolated from the petroleum layer. Distillation gave (+)-carvomenthene (5·06 g., 77%), b. p. 59°/11 mm., n_D^{25} 1·4544, $[\alpha]_D$ +114°. The selective hydrogenation of limonene has recently been reported [9] to give carvomenthene with n_D^{23} 1·4557, $[\alpha]_D$ +109°.

Reaction of (+)-*Carvomenthene with Mercuric Acetate.*—Solutions of crude carvomenthene (9 g.) in dioxan (40 c.c.; distilled from sodium) and mercuric acetate (20·72 g.) in water (200 c.c.) were mixed and then stirred vigorously. 2N-Sodium hydroxide was added in portions to neutralise from time to time the acetic acid formed in the reaction. Some yellow mercuric oxide was precipitated if too large a portion of alkali was added, but this redissolved as more acetic acid was formed from the reaction. After 4 hr., one mol. of alkali (35 c.c.) had been added and addition of a further small portion gave no yellow precipitate. The cream-coloured emulsion was kept at 20° overnight, and then treated with 2N-sodium hydroxide (140 c.c.) to dissolve the mercurial. The solution was filtered and sodium chloride (7·61 g.) was dissolved in the filtrate into which carbon dioxide was then passed to neutralise the alkali and hence to precipitate the crude mercurial (19·45 g.; dried over P_2O_5). Extraction with hot benzene

[6] Wallach, *Annalen*, 1906, **350**, 158.
[7] *Idem*, *ibid.*, 1911, **381**, 58.
[8] B.P. 761,686/1956.
[9] Newhall, *J. Org. Chem.*, 1958, **23**, 1274.

(120 c.c.) left a residue (2 g.) of inorganic material, and the yield of organomercurial was therefore 17·45 g. (69%). (By further working up of residues and mother-liquors, the yield of crude mercurial could be raised to 94%.) The cooled benzene solution gave the mercurial (14·3 g.) as needles, m. p. 134—136°. Recrystallisation from light petroleum (b. p. 80—100°) gave (80% recovery) pure 2α-*chloromercuri*-1α-*methyl*-4β-iso*propyl*cyclo*hexan*-1β-*ol* (V), m. p. 135—136°, $[\alpha]_D$ +27° (Found: C, 30·9; H, 4·9. $C_{10}H_{19}OClHg$ requires C, 30·7; H, 4·9%).

By starting with purified carvomenthene (above) the yield of mercurial (after the stage of extraction with benzene) was raised from 69 to 74%.

Reduction of the Mercurial (V).—A mixture of the pure mercurial (3·91 g.), 3% sodium hydroxide solution (40 c.c.), and 90% hydrazine hydrate (3·6 c.c.) was heated under reflux for 48 hr. The yield of mercury was 1·51 g. (75%) and subsequent study of the remainder of the products also indicated that reduction was not complete. The organic products were isolated with pentane, evaporation of which gave a residue which partially solidified owing to the presence of some organomercurial. Distillation at 0·4 mm. with a bath-temperature of 20—110° gave carvomenthene and *trans-p*-menthanol (0·68 g. combined), some of the former being collected in a cold trap. (The product obtained by raising the bath-temperature above 120° was partly ketonic and arose from the thermal decomposition of organomercurial still present.) The olefin–alcohol mixture was shown (by infrared and vapour-phase chromatographic analyses) to consist of carvomenthene (0·25 g., 18%) and *trans-p*-menthanol (VI) (0·43 g., 28%). The alcohol was isolated from the mixture by vapour-phase chromatography, and gave an infrared spectrum identical in all detail with that of *trans-p*-menthanol prepared by hydrogenation of *trans*-β-terpineol (below). It also gave the same phenylurethane, m. p. and mixed m. p. 102—104°.

The mercurial (3·91 g.) was reduced with sodium amalgam (139·1 g.; 3% of Na) and water (25 c.c.) at 0°. The mixture was finally kept at 0° for two days and then the organic product was isolated with pentane. Distillation gave carvomenthene (0·83 g., 60%), b. p. 64—66°/17 mm., n_D 1·4538, infrared spectrum identical with that of the authentic compound.

cis- *and* trans-p-*Menthanol* (X and VI).—*cis*-β-Terpineol (IX) (m. p. 36°; 0·156 g.) and phenyl *iso*cyanate (0·146 g.) were heated together in a sealed tube at 80° for 7 hr. The insoluble diphenylurea was left behind on extraction with light petroleum (b. p. 60—80°). Filtration of the extract through deactivated alumina gave the crude urethane (0·153 g.), m. p. 58—65°. Recrystallisation from aqueous methanol and from light petroleum (b. p. 40—60°) gave the *phenylurethane*, m. p. 69—70° (Found: C, 75·1; H, 8·4. $C_{17}H_{23}O_2N$ requires C, 74·7; H, 8·5%).

cis-β-Terpineol (0·616 g.) in ethanol (10 c.c.) was shaken with hydrogen in the presence of Adams catalyst (31 mg.). Hydrogenation ceased (30 min.) when 83 c.c. had been absorbed (at 22°/767 mm.). Isolation with pentane gave *cis-p*-menthanol (X), m. p. 43—44°, which by the technique above gave a *phenylurethane*, m. p. 85° (from pentane) (Found: C, 74·3; H, 9·1. $C_{17}H_{23}O_2N$ requires C, 74·15; H, 9·15%).

trans-β-Terpineol (VIII) gave a phenylurethane, m. p. 82—83° (lit., m. p. 85°). Hydrogenation of *trans*-β-terpineol (as for the *cis*-compound) gave *trans-p*-menthanol (VI) (85%), b. p. 98—99°/19 mm., n_D^{25} 1·4568. Its phenylurethane had m. p. 102—103° (lit., m. p. 101°).

Spectra.—The spectra (see Table) were determined with 5% solutions of the compounds in " AnalaR " carbon disulphide.

Absorption bands in the 900—1200 *cm.*$^{-1}$ *region for tertiary alcohols.*

tert.-Butyl alcohol	912				1140	1195
1-Methyl*cyclo*hexanol	914		972		1133	1175
cis-p-Menthanol (X)	915		981		1120	1150
trans-p-Menthanol (VI)	907	941	988	1000	1084	1167
cis-β-Terpineol (IX)	916		982		1110	1145
trans-β-Terpineol (VIII)	911	930	952	1000	1100	1150

The authors have pleasure in thanking Gallahers Ltd., Belfast, for financial assistance (to R. S. M.), Mr. M. F. Carroll, Mr. R. L. Blackmore, and Mr. D. Wood (A. Boake, Roberts & Co. Ltd.) for samples and for chromatographic analyses, and Mr. J. Henry and Mr. J. Austin of this Department for other analyses.

THE QUEEN'S UNIVERSITY OF BELFAST. [*Received, January* 13*th*, 1959.]

XUM

364. *Silver–Silver Sulphide Electrodes in Alkaline Solutions.*

By R. M. Golding.

From e.m.f. measurements at 25° on the cell,
$Ag,Ag_2S|S^{2-}$ $(m_s)||OH^-(m_1)||OH^-(m_1)|H_2(1\ atm.)Pt$
the sulphide electrode was found to be irreversible in alkaline solution, obeying the equation $e_0 = b + (RT/nF)\ \ln m_s$ where $b = 0{\cdot}691$ v and $n = 1{\cdot}61$. The sulphide concentration, m_s, ranged from 10^{-3} to 10^{-6} molal.

Goates *et al.*[1] recently found the standard e.m.f. ($e_0°$) of the $Ag,Ag_2S|S^{2-}$ electrode to be 0·7125 volt in slightly alkaline solutions. They assumed the electrode reaction to be $2Ag + S^{2-} \longrightarrow Ag_2S + 2e$. They used the cell $Ag,Ag_2S|S^{2-}$ (x molal)‖normal calomel; the e.m.f. of the $Ag,Ag_2S|S^{2-}$ half cell was given by the Nernst equation as $\varepsilon = \varepsilon° + (RT/nF)\ \ln a_s$. Sodium sulphide solutions were used and the activity of the sulphide ion was calculated from the hydrolysis equilibrium. From four sodium sulphide concentrations (0·1—0·005 molal) the standard e.m.f. of the $As,Ag_2S|S^{2-}$ electrode was evaluated.

Using a wide range of S^{2-} and OH^- concentrations, we could not obtain results that would correspond to a reversible two-electron process ($n = 2{\cdot}0$). This led to a more detailed study of the electrode system in alkaline solutions.

Experimental

The cell detailed above was set up, the same hydroxyl-ion concentrations being used on each side of the liquid–liquid junction, so that the liquid–liquid potentials could be ignored. The cell was H-shaped, divided into three compartments. The vertical tubes were separated from the central horizontal tube by solid filter-paper plugs. Standardised hydroxide was added to the three compartments, and dry nitrogen passed through to remove all traces of oxygen from the solution to which the sulphide was to be added. The central hydroxide compartment minimised diffusion of sulphide through the cell.

The silver–silver sulphide electrode was prepared by silver-plating a spiral of platinum wire. The silver surface was washed in ammonia solution and then hydrochloric acid, placed in an atmosphere of hydrogen sulphide for 30 min., dried, and finally washed in distilled water. The electrodes were kept under distilled water until used.[2]

Carbonate-free sodium hydroxide solutions of various molalities were used. Pure hydrogen sulphide was bubbled through oxygen-free alkali solutions and the HS^- concentration determined by measuring the optical density of the solutions at 2300 Å ($\lambda_{max.}$ HS^- = 2300 Å, and $\varepsilon_{max.} = 7{\cdot}98 \times 10^3$).[3] The sulphide-ion concentration was evaluated, with allowance for hydrolysis, from the concentration dissociation constant,[3] $[H^+][S^{2-}]/[HS^-] = 1{\cdot}0 \times 10^{-14}$. All the e.m.f. readings were taken at 25° after the cell had reached equilibrium (usually 12 hr.).

Results.—From the e.m.f. readings the potential of the sulphide electrode was obtained relative to the standard hydrogen electrode:

$$e_0 = \varepsilon + 0{\cdot}0592 \log m_{OH}\gamma_{OH}/10^{-14}$$

where e_0 is the e.m.f. relative to standard potential of the hydrogen electrode, ε the e.m.f. measured, m_{OH} = sodium hydroxide molality, and γ_{OH} = activity coefficient (assumed equal to the mean molal activity coefficient $\gamma_\pm$ for NaOH).

From Robinson and Stokes's data,[4] $\gamma_{NaOH} = 0{\cdot}681$, 0·690, and 0·723 for 1·20M-, 0·500M-, and 0·250M-NaOH respectively, and calculation from the Debye–Hückel theory gives $\gamma_{NaOH} = 0{\cdot}891$ for $1{\cdot}20 \times 10^{-2}$M-NaOH.

From the Table of results, by the method of least squares, for the range of sulphide concentrations 10^{-6} to 10^{-3}m, $e_0 = 0{\cdot}691 + (RT/1{\cdot}61F)\ \log m_s$, with a regression coefficient of 0·997.

[1] Goates, Cole, Gray, and Faux, *J. Amer. Chem. Soc.*, 1951, **73**, 707.
[2] Martinez, *Chem. Abs.*, 1941, **42**, 4072.
[3] Ellis and Golding, *J.*, 1959, 127.
[4] Robinson and Stokes, "Electrolyte Solutions," Butterworths Scientific Publications, London, 1955, p. 477.

$-e$	m_{OH}	$-\log m_s$	e_0	b (n = 1·61)	$-e$	m_{OH}	$-\log m_s$	e_0	b (n = 1·61)
0·2266	1·20	2·530	0·5989	0·692	0·2753	0·500	4·238	0·5272	0·683
0·2265	1·20	2·491	0·5970	0·689	0·1902	0·250	2·580	0·5948	0·689
0·2380	1·20	2·993	0·5855	0·696	0·1964	0·250	2·921	0·5886	0·696
0·2496	1·20	3·219	0·5739	0·692	0·2265	0·250	3·634	0·5585	0·689
0·2664	1·20	3·665	0·5571	0·692	0·1940	0·0120	4·668	0·5185	0·690
0·2850	1·20	4·019	0·5385	0·686	0·2076	,,	5·070	0·5049	0·693
0·1964	0·500	2·261	0·6061	0·689	0·2231	,,	5·590	0·4894	0·670
0·2300	0·500	3·171	0·5725	0·689	0·2275	,,	5·590	0·4850	0·691

However, the Nernst equation gives

$$e_0 = e_0^\circ + (RT/nF) \ln m_s \gamma_s = e_0^\circ + (RT/nF) (\ln \gamma_s + \ln m_s)$$

Comparing this equation with the experimental result, we have

$$e_0^\circ + (RT/nF) \ln \gamma_s = 0{\cdot}691 \ (= b)$$

and since e_0° is a defined cell constant, γ_s must be constant, within the experimental error, over the sulphide and hydroxide concentrations used.

Conclusion.—This experimentally derived equation, with an apparent value of $n = 1{\cdot}61$, shows that the electrode reaction $Ag,Ag_2S|S^{2-}$ in alkaline solution is irreversible.

In e.m.f. cell work, it is important to show that the cell reaction being considered is a thermodynamically reversible or irreversible process. If it is reversible, the number of electrons involved will be an integer and the free-energy change, ΔG, of such a system can be evaluated from the equation $\Delta G = ne_0^\circ F$. If the number of electrons involved in the cell reaction is not an integer the electrode process is irreversible and the free-energy change cannot be evaluated.

As the $Ag,Ag_2S|S^{2-}$ cell reaction in alkaline solutions is irreversible, the free energy of formation of Ag_2S cannot be derived. From a series of only four e.m.f. readings in alkaline solutions Goates *et al.*[1] assumed that the electrode process was reversible and therefrom calculated the free energy of formation of Ag_2S. The present results show that this was not justified.

Despite the irreversibility of the electrode the experimentally derived equation relating e.m.f. and sulphide-ion concentration enables the latter to be measured at high alkalinities. As the electrode is reproducible it can also be used as a reference electrode for the study of sulphide systems.

The author is indebted to A. J. Ellis for helpful suggestions and comments, and to H. P. Rothbaum for the successful cell design.

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Wellington, New Zealand.

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365. *An Examination of the Rutaceae of Hong Kong. Part II.*[1] *The Alkaloids, Nitidine and Oxynitidine, from* Zanthoxylum nitidum.

By H. R. Arthur, (Miss) W. H. Hui, and (Miss) Y. L. Ng.

Nitidine and oxynitidine, two new benzophenanthridine alkaloids, have been isolated from *Zanthoxylum nitidum*. Unlike the other alkaloids of this class, these compounds are substituted in the 6 : 7 : 2′ : 3′-positions.

Zanthoxylum nitidum (Lam.) DC. (*Fagara nitida*), known locally as *Ju ti chin niu* (golden cow in the soil), a woody climber with yellow root and small white flowers, grows in most areas of Hong Kong Colony. An investigation of the bacteriostatic properties of the Formosan plant has been reported,[2] and in Part I [1] we showed that diosmin occurred in the root bark.

An alkaloid, oxynitidine, and a salt of a related quaternary alkaloid, nitidine, have now been isolated from the methanol extracts of the root bark and root wood. Oxynitidine is insoluble in water and thus was separated from the quaternary salt when the mixture as isolated was boiled with water. Basification of the aqueous salt solution produced two compounds dihydronitidine, $C_{21}H_{19}O_4N$, and oxynitidine, $C_{21}H_{17}O_5N$ by disproportionation. Since dihydronitidine was easily oxidised by air it was separated from oxynitidine by chromatography under argon.

Each of these compounds contained two methoxyl groups and one methylenedioxy-group (positive Labat test); on mild oxidation dihydronitidine gave oxynitidine, the reverse process being effected by reduction. Dihydronitidine formed salts; oxynitidine did not, and hence it was considered that the fifth oxygen atom of oxynitidine was present in a substituted amide function. Thus dihydronitidine was isomeric with, and contained the same functional groups as, dihydrochelerythrine (I). Oxynitidine appeared to be similarly related to oxychelerythrine (II).

Although distillations with zinc and fusions with zinc and zinc chloride gave no evidence that these two compounds were benzophenanthridine derivatives, the general chemical properties of both suggested that they were; further, the ultraviolet spectrum of dihydronitidine resembled closely that of dihydrochelerythrine.

Dihydronitidine and oxynitidine were shown not to be related to dihydrochelerythrine and oxychelerythrine simply by interchange of the substituent methoxyl groups with that of the methylenedioxy-group since the tetramethoxy-compound (A), obtained from oxynitidine, was not identical with the tetramethoxybenzophenanthridone (III), obtained by oxidation of 9 : 10-dihydro-7 : 8 : 2′ : 3′-tetramethoxy-10-methyl-1 : 2-benzophenanthridine [3] (IV), the reference compound for the chelerythrine–sanguinarine group of alkaloids synthesised [4] in 1950.

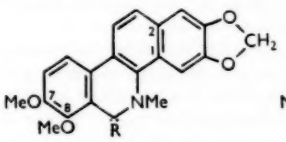
However, degradative oxidation of oxynitidine, which was difficult to control, gave *N*-methyl-*m*-hemipinimide. This suggested that the methoxyl groups of our bases were substituted in the 6 : 7-positions of the benzophenanthridine skeleton, instead of in the 7 : 8-positions as in the chelidonine group of alkaloids. This view, which was supportable on biogenetic grounds, was confirmed thus: the methosulphate of 6 : 7 : 2′ : 3′-tetramethoxybenzophenanthridine [4] was reduced to give 9 : 10-dihydro-6 : 7 : 2′ : 3′-tetramethoxy-10-methyl-1 : 2-benzophenanthridine (V) which was shown to be identical with the reduction product (B) of the tetramethoxy-compound (A) obtained from oxynitidine. Thus compound A must be represented by formula (VI), and oxynitidine is therefore 6 : 7-dimethoxy-10-methyl-2′ : 3′-methylenedioxy-1 : 2-benzophenanthridone (VII). The structure of the other alkaloid, nitidine (6 : 7-dimethoxy-10-methyl-2′ : 3′-methylenedioxy-1 : 2-benzophenanthridinium hydroxide) (VIII), and that of the transformation product,

[1] (*a*) Part I, *J.*, 1956, 632; (*b*) cf. also Arthur, Hui, and Ng, *Chem. and Ind.*, 1958, 1514.
[2] Yang, Chang, and Weng, *J. Formosan Med. Assoc.*, 1953, **52**, 109.
[3] Späth and Kuffner, *Ber.*, 1931, **64**, 2034.
[4] Bailey, Robinson, and Staunton, *J.*, 1950, 2277.

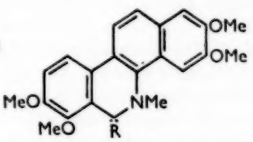
dihydronitidine (9 : 10-dihydro-6 : 7-dimethoxy-10-methyl-2′ : 3′-methylenedioxy-1 : 2-benzophenanthridine) (IX), follow.

The yellow water-soluble quaternary salt of nitidine obtained from the plant could not be purified nor could nitidine itself be obtained from it, since basification of the salt solution, or subjecting a solution of it to ion-exchange or chromatography, caused disproportionation. Nitidine, however, has been characterised as the ψ-cyanide since this compound is readily prepared from an aqueous solution of the naturally occurring salt. Nitidine has also been characterised as the acetate, chloride, iodide, and periodide.

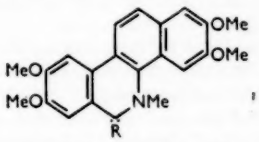
Owing to the ease of aerial oxidation of solutions of dihydronitidine salts to the corresponding nitidine salts, we at first mistook nitidine chloride and nitidine iodide for salts of dihydronitidine. Thus the hydriodide and hydrochloride reported in our preliminary note [15] are actually the iodide and the chloride. Both nitidine iodide and nitidine chloride on being heated yield a compound, $C_{20}H_{15}O_4N$, m. p. 285—286°. We have evidence that this compound may not be the expected 6 : 7-dimethoxy-2′ : 3′-methylenedioxybenzophenanthridine, and it is being further investigated. The authentic dihydronitidine hydrochloride and dihydronitidine hydrogen sulphate have been prepared under argon.



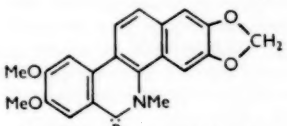
(I) R = H_2. (II) R = O



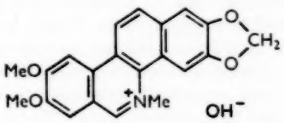
(III) R = O. (IV) R = H_2



(V) R = H_2. (VI) R = O



(VII) R = O (IX) R = H_2



(VIII)

The benzophenanthridine alkaloids previously reported are listed by Manske and Holmes.[5] All are substituted in the 7 : 8 : 2′ : 3′-positions whereas nitidine and oxynitidine are substituted in the 6 : 7 : 2′ : 3′-positions, and this seems to be the first reported certain variation in substitution, although methoxychelidonine, of undetermined structure, could be trisubstituted in the 6 : 7 : 8-positions.

A benzophenanthridine alkaloid (chelerythrine) was reported,[6] for the first time from a *Zanthoxylum* species, in 1953.

Since small amounts of oxynitidine are obtainable from plant extracts which were neither treated with alkali nor chromatographed we have called oxynitidine an alkaloid. It could, however, be an artefact.

Experimental

Analyses were by Dr. Zimmermann, Melbourne. The alumina used for chromatography was B.D.H. analysis grade. Light petroleum refers to the fraction, b. p. 60—80°. Unless otherwise stated, m. p.s were taken on a Kofler block; where stated to have been taken on a gas-heated copper block the m. p.s are uncorrected.

Isolation of Products.—(a) *Root bark.* Milled root bark (3 kg.) was extracted with hot methanol (17 l.) for 25 hr. The extract was concentrated to ½ l., then left for a few days. The yellow crystalline mixture (4·0 g.) was collected, then extracted with boiling water. The residue (0·8 g.) contained oxynitidine; basification of the aqueous extract with ammonia gave a buff-coloured precipitate (2·5 g.).

[5] Manske and Holmes, "The Alkaloids," New York, Academic Press, 1954, Vol. IV, 253.
[6] Cannon, Hughes, Ritchie, and Taylor, *Austral. J. Chem.*, 1953, **6**, 86.

(b) *Root wood.* Milled root (2 kg.) was extracted and worked-up as stated under (a); a buff-coloured precipitate (3·0 g.) was obtained.

Separation of Oxynitidine (VII) *and Dihydronitidine* (IX).—The buff-coloured precipitate (3·0 g.) was dissolved in hot benzene. The brownish rosettes (0·5 g.) which separated gave, after two recrystallisations from ethanol, colourless fine silky needles of *oxynitidine*, m. p. 284—285°, $[\alpha]_D^{20}$ 0·0° (*c* 0·43 in $CHCl_3$) (Found: C, 69·4; H, 4·7; N, 3·6; OMe, 16·0; NMe, 7·1. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7; N, 3·9; 2OMe, 17·1; 1NMe, 7·9%), $\lambda_{max.}$ in ethanol (log ε in parentheses) 367 (3·63), 333 (4·18), 320 (4·20), 288 (4·81), 277 (4·72), 251 mμ (4·59). (Solutions of oxynitidine had a purple fluorescence in ultraviolet light. With concentrated sulphuric acid, oxynitidine gave a red colour which became purple on warming of the solution.) The benzene filtrate was chromatographed on alumina (250 g.) under argon. Elution with benzene gave a product (0·8 g.) which after recrystallisation from ethanol under argon yielded colourless elongated prisms of *dihydronitidine*, m. p. 221—223°, $[\alpha]_D^{15}$ 0·0° (*c* 0·49 in $CHCl_3$) (Found: C, 71·5; H, 5·6; N, 4·2; OMe, 17·2; NMe, 7·3%; *M*, 363. $C_{21}H_{19}O_4N$ requires C, 72·2; H, 5·5; N, 4·0; 2OMe, 17·8; 1NMe, 8·3%; *M*, 349), $\lambda_{max.}$ in ethanol (log ε in parentheses) 311 (4·29), 278 (4·54), 228 mμ (4·61). (Solutions of dihydronitidine had a blue fluorescence in ultraviolet light; they rapidly changed from colourless to yellow in air. With concentrated sulphuric acid dihydronitidine gave a colour identical with that from oxynitidine.) Elution with benzene–chloroform (3 : 2) gave oxynitidine (0·7 g.), m. p. 284—285° after two recrystallisations from ethanol.

Salts of Dihydronitidine.—(a) *The hydrogen sulphate.* Dihydronitidine (0·3 g.) was dissolved in chloroform (10 ml.), and the solution was shaken under argon with 6N-sulphuric acid (10 ml.) in a separatory funnel. A white precipitate of the *hydrogen sulphate* (0·4 g.) which was formed at the interface was collected under argon and washed with ethanol under argon. It had m. p. 290—292° (decomp.) (gas-heated copper block) (Found: C, 50·4; H, 5·5; N, 2·8; S, 6·3. $C_{21}H_{19}O_4N,H_2SO_4,3H_2O$ requires C, 50·3; H, 5·4; N, 2·8; S, 6·4%).

(b) *Hydrochloride.* Dihydronitidine (0·2 g.) was dissolved in chloroform (10 ml.), and concentrated hydrochloric acid (2 ml.) was added. No precipitate was observed. When the chloroform was distilled under argon, the colourless needles (0·25 g.) which separated were collected under argon and washed with ethanol under argon. The *hydrochloride* had m. p. 215—216° (decomp.; vac.) (gas-heated copper block) (Found: C, 56·0; H, 6·0; N, 3·0; Cl, 8·1. $C_{21}H_{19}O_4N,HCl,4H_2O$ requires C, 55·1; H, 6·0; N, 3·1; Cl, 7·8%).

The above two colourless salts in the solid state or in solution rapidly became yellow; their solutions then gave a precipitate with potassium cyanide solution.

(c) *Methiodide.* Dihydronitidine methiodide was difficult to obtain. After several attempts at preparation, all of which failed to give a pure product, the following method was adopted: dihydronitidine (0·05 g.) was heated with methyl iodide (70 ml.) in a sealed tube for 2 weeks on the steam-bath. Distillation of the methyl iodide left an orange methiodide which after crystallisation from methanol under argon separated as orange needles, m. p. 268° (Found: C, 55·0; H, 4·2; N, 3·0. Calc. for $C_{21}H_{19}O_4N,CH_3I$: C, 53·8; H, 4·5; N, 2·9%). This product dissolved readily in water and had a sharp m. p.; we were unable to obtain a purer product.

Dihydronitidine from Oxynitidine.—(*a*) Oxynitidine (0·7 g.) was dissolved in hot phosphorus oxychloride (10 ml.), and the solution was heated at 105—110° for 3 hr.; excess of phosphorus oxychloride was removed at reduced pressure and water was added to the residue. A yellow precipitate (0·65 g.), m. p. 230—235°, was formed. This crude product was added gradually to a suspension of zinc dust in hot 3N-hydrochloric acid. The yellow colour disappeared. The mixture was filtered hot and the precipitate formed on cooling was extracted with chloroform. Removal of the chloroform gave a brown residue (0·3 g.) which crystallised from ethanol. Yellow needles, which, on further recrystallisation had m. p. 283—286° (after becoming colourless at about 240°) (gas-heated copper block), of nitidine chloride, separated. The mother-liquor deposited light brown prisms, m. p. 213—220°, which, after chromatography in benzene over alumina and recrystallisation from ethanol gave colourless elongated prisms of dihydronitidine, m. p. 220—222° (Found: C, 72·1; H, 5·3; N, 3·9; OMe, 17·9%).

(*b*) Oxynitidine (0·5 g.) was dissolved in toluene (120 ml.). Zinc amalgam (5 g.), water (20 ml.), and concentrated hydrochloric acid (40 ml.) were added, and the mixture was boiled under reflux for 10 hr. with occasional addition of zinc amalgam and hydrochloric acid. The aqueous layer was extracted with chloroform, from which extract a trace of dihydronitidine, m. p. 218—221°, was obtained. Oxynitidine was recovered from the toluene.

(*c*) To oxynitidine (0·5 g.) dissolved in sodium-dried tetrahydrofuran (50 ml.), lithium aluminium hydride (0·25 g.) was added. The mixture was heated under reflux in an atmosphere of argon for 3 hr. A little dilute hydrochloric acid was added, and then the organic phase was separated and diluted with water. The colourless precipitate was collected and after recrystallisation from ethanol yielded elongated prisms (0·4 g.), m. p. 220—222°, alone or in admixture with dihydronitidine.

Oxynitidine from Dihydronitidine.—To a solution of dihydronitidine hydrochloride (0·1 g.) in hot water (20 ml.) was added a hot solution (10 ml.) of potassium ferricyanide (0·2 g.) and potassium hydroxide (0·1 g.). The precipitate (0·08 g.) which was formed immediately was collected and recrystallised from ethanol. Colourless needles, m. p. 283—285°, alone or in admixture with oxynitidine, were obtained.

Salts of Nitidine.—(a) *Acetate.* Dihydronitidine (0·5 g.) was dissolved in hot 50% acetic acid (100 ml.). Mercuric acetate (2·0 g.) was added and the mixture was heated on the steam-bath for 2 hr. Precipitation began in the hot solution. The precipitate was collected after the solution cooled and hydrogen sulphide was passed into the mother-liquor. The black mixture obtained was filtered and sodium acetate was added to the filtrate. The organic product, which was salted out, was collected, and on recrystallisation from alcohol it deposited yellow needles of *nitidine acetate* (0·2 g.), m. p. 255—260° (Found: C, 58·1; H, 6·1; N, 3·0. $C_{23}H_{21}O_6N,4H_2O$ requires C, 57·6; H, 6·1; N, 2·9%). This product was very soluble in cold water, and the aqueous solution gave a colourless precipitate with potassium cyanide solution. An aqueous solution of nitidine acetate was basified with ammonia. From the precipitate so obtained, dihydronitidine, m. p. 218—220°, and oxynitidine, m. p. 280—282°, were isolated by the chromatographic method used to separate these two products from the precipitate obtained on basifying the crude nitidine salt from the plant.

(b) *Chloride.* Dihydronitidine (0·6 g.) was dissolved in ethanol (800 ml.). Concentrated hydrochloric acid (3 ml.) was added and the mixture, open to the air, was warmed on the water-bath for ½ hr. The solution was concentrated and a very pale yellow precipitate (0·4 g.) consisting of prisms and needles appeared on cooling. Repeated recrystallisation of this product from ethanolic hydrochloric acid gave bright yellow needles of *nitidine chloride* (Found: C, 60·8; H, 5·3; N, 3·6; Cl, 8·8. $C_{21}H_{18}O_4NCl,2H_2O$ requires C, 60·1; H, 5·1; N, 3·3; Cl, 8·5%). The mother-liquor (above) on concentration gave the same product as bright yellow needles.

(c) *Iodide.* A solution of dihydronitidine in ethanol was treated with hydriodic acid. The *product* was isolated as yellow needles in the way stated for the chloride (Found: C, 52·4; H, 4·0; NMe, 6·6; I, 25·4. $C_{21}H_{18}O_4NI$ requires C, 53·1; H, 3·8; 1NMe, 7·0; I, 26·7%).

Both nitidine chloride and nitidine iodide, on being heated to about 240°, changed to colourless needles of a *substance*, m. p. 285—286° (Found: C, 72·1; H, 4·6; N, 4·4. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5; N, 4·2%).

(d) *ψ-Cyanide.* The yellow crystalline mixture (0·2 g.) obtained from the methanol extract of the plant was dissolved in water. Potassium cyanide solution was added. The colourless precipitate (0·1 g.) was collected and recrystallised from benzene. Plates of the *ψ-cyanide*, m. p. 215—216°, m. p. 234° (decomp.; vac.) (gas-heated copper block), were deposited (Found: C, 70·6; H, 4·9; N, 7·6; OMe, 16·2. $C_{22}H_{18}O_4N_2$ requires C, 70·6; H, 4·8; N, 7·5; 2OMe, 16·6%). This product was obtained likewise from nitidine chloride.

(e) *Periodide.* To a boiling solution of dihydronitidine (0·3 g.) in ethanol (400 ml.) was added a solution of iodine (1·0 g.) in ethanol. Dark red-brown needles (0·5 g.) of *nitidine periodide*, m. p. 292—294°, raised by recrystallisation from acetone to m. p. 300—301° (decomp.) (gas-heated copper block), were formed (Found: C, 35·1; H, 2·6; I, 51·3. $C_{21}H_{15}O_4NI_3$ requires C, 34·6; H, 2·5; I, 52·2%). Prolonged heating of the periodide in acetone gave nitidine iodide.

6 : 7 : 2′ : 3′-*Tetramethoxy*-10-*methyl*-1 : 2-*benzophenanthrid*-9-*one* (A).—Phloroglucinol (2·7 g.) was dissolved in 50% sulphuric acid (150 ml.). Oxynitidine (2·5 g.) was added to the hot solution which was boiled for ½ hr., then heated on a steam-bath for 5 hr. Then an equal volume of water was added, and the mixture was left overnight. A deep reddish precipitate (3·0 g.) was deposited, which, after removal of some red insoluble material, yielded on several crystallisations from ethanol, fine light brown needles, m. p. 292—294°, which gave a deep greyish-green colour with ferric chloride solution and a negative Labat methylenedioxy-test. This product was methylated with diazomethane in ether during one week, fresh diazomethane being added

daily. (Later, a smooth methylation in tetrahydrofuran for 12 hr. was found superior.) The *product*, after two recrystallisations from ethanol, separated as needles, m. p. 251—253° (Found: C, 69·6; H, 5·6; OMe, 32·9. $C_{22}H_{21}O_5N$ requires C, 69·6; H, 5·6; 4OMe, 32·7%).

9 : 10-*Dihydro*-6 : 7 : 2′ : 3′-*tetramethoxy*-10-*methyl*-1 : 2-*benzophenanthridine* (B).—(*a*) The tetramethoxy-*N*-methylbenzophenanthridone (0·3 g.) and phosphorus oxychloride (7 ml.) were boiled under reflux on an oil-bath for 3 hr. The yellow precipitate obtained when this mixture was poured into water was suspended in 30% hydrochloric acid (40 ml.). Zinc (2·0 g.) was added and the mixture was heated on the steam-bath for 6 hr. with occasional addition of zinc and hydrochloric acid. The product was extracted with chloroform and finally crystallised from methanol. As it did not melt sharply, it was boiled in methanol with sodium borohydride (0·3 g.) for 1 hr. After isolation by the usual procedure the product was recrystallised from methanol. Colourless prisms (0·1 g.), m. p. 216—218°, of 9 : 10-*dihydro*-6 : 7 : 2′ : 3′-*tetramethoxy*-10-*methyl*-1 : 2-*benzophenanthridine* (B) separated (Found: C, 72·1; H, 6·3; OMe, 33·7. $C_{22}H_{23}O_4N$ requires C, 72·3; H, 6·3; 4OMe, 34·0%). This product was unchanged after chromatography in benzene on alumina.

(*b*) Lithium aluminium hydride (0·25 g.) was added to the tetramethoxy-*N*-methylbenzophenanthridone in tetrahydrofuran, and the mixture under argon was boiled under reflux on the steam-bath for 3 hr. A little dilute hydrochloric acid was added and then the supernatant liquid was decanted and evaporated to dryness under argon. On recrystallisation of the residue from ethanol, lozenge-shaped crystals, m. p. 216—218° alone or in admixture with the product (B) from (*a*), were obtained.

(*c*) The methosulphate of 6 : 7 : 2′ : 3′-tetramethoxy-1 : 2-benzophenanthridine (0·3 g.) was suspended in 3% hydrochloric acid (45 ml.) with zinc (6·0 g.). The mixture was boiled under reflux for 8 hr. during which concentrated hydrochloric acid (3·0 ml.) was added after each 2-hourly interval; the yellow salt dissolved. A pale yellow precipitate appeared after the mixture had been cooled at 0—5° overnight. This was collected and treated with 5N-ammonia, and the mixture was then extracted with chloroform. The chloroform extract was washed with water, dried ($MgSO_4$), and then evaporated to dryness under argon. The residue (0·06 g.) was crystallised from ethanol. Lozenge-shaped crystals of compound (V), m. p. 211—212°, raised to m. p. 216—218·5° on further recrystallisation from ethanol, were obtained (Found: C, 72·1; H, 6·2; N, 4·1; OMe, 33·9%). This product did not depress the m. p. of product (B) from (*a*). The products had identical infrared spectra.

9 : 10-*Dihydro*-7 : 8 : 2′ : 3′-*tetramethoxy*-10-*methyl*-1 : 2-*benzophenanthridine* (IV).—Chelerythrine chloride (1·0 g.) was converted into dihydrochelerythrine (0·6 g.) and this was demethylenated and then methylated as given under the preparation of 6 : 7 : 2′ : 3′-tetramethoxy-10-methyl-1 : 2-benzophenanthridone. After recrystallisation from ethanol it had m. p. 190—192° (Späth and Kuffner [3] give m. p. 182—183°; Bailey, Robinson, and Staunton [4] give m. p. 183·5—185°). Its m. p. was depressed to 180—190° in admixture with 9 : 10-dihydro-6 : 7 : 2′ : 3′-tetramethoxy-10-methyl-1 : 2-benzophenanthridine.

7 : 8 : 2′ : 3′-*Tetramethoxy*-10-*methyl*-1 : 2-*benzophenanthridone* (III).—The preceding product (0·5 g.) was treated with alkaline potassium ferricyanide as stated for the oxidation of dihydronitidine. The *product* (0·4 g.) on recrystallisation from ethanol had m. p. 223—225° (Found: C, 69·7; H, 5·8; N, 3·7; OMe, 32·9; NMe, 6·6. $C_{22}H_{21}O_5N$ requires C, 69·7; H, 5·5; N, 3·7; 4OMe, 32·7; 1NMe, 7·5%). Its m. p. was depressed to 218—230° on admixture with 6 : 7 : 2′ : 3′-tetramethoxy-10-methyl-1 : 2-benzophenanthridone.

N-*Methyl*-m-*hemipinimide*.—(*a*) Oxynitidine (0·5 g.) was dissolved in hot stabilised glacial acetic acid (250 ml.), and a 5% aqueous solution (50 ml.) of potassium permanganate was added during 15 min. After it was cooled the mixture was decolorised with sulphur dioxide. The inorganic salts were collected and the yellow filtrate was evaporated to dryness under reduced pressure. The residue thus obtained was extracted with boiling benzene (3 × 400 ml.). The combined benzene extracts were concentrated to 100 ml. and then diluted with an equal volume of light petroleum (b. p. 40—60°). This solution was then chromatographed on alumina. Elution with benzene–petroleum (1 : 1) gave in the first fractions (400 ml. of eluate) a product (0·014 g.) which separated on recrystallisation from ethanol as colourless prisms, m. p. 215—216° (decomp.), m. p. 254—256° (vac.) (gas-heated copper block) of *N*-methyl-*m*-hemipinimide (Found: C, 59·5; H, 4·8; N, 7·1; OMe, 26·9. Calc. for $C_{11}H_{11}O_4N$: C, 59·7; H, 5·0; N, 6·3; 2OMe, 28·0%). In ultraviolet light this product, in solution, had a purple fluorescence, and, on the chromatographic column, a green fluorescence. Continued elution gave in the next

300 ml. of eluate a product, m. p. 272°, which gave a positive test for methylenedioxy-groups and had no fluorescence in ultraviolet light. It was not further investigated.

(*b*) By the method of Edwards *et al.*,[7] veratraldehyde was converted into veratric acid, and the latter was converted into *m*-meconine. Oxidation of *m*-meconine gave *m*-hemipinic acid. This acid (0·5 g.) was heated at 175—185° for 20 min., and the anhydride so obtained was dissolved with fused sodium acetate (1·5 g.) and methylamine hydrochloride (0·8 g.) in glacial acetic acid. The mixture was heated under reflux for 20 min., then allowed to cool. The inorganic salts which separated were collected, and from the filtrate the crude product separated on cooling. This was filtered through alumina and then recrystallised from ethanol. Colourless prisms, m. p. 256—258° (vac.) (gas-heated copper block) alone or in admixture with the product from (i), separated (Found: C, 59·7; H, 5·0; N, 6·3; OMe, 27·8%). The products (*a*) and (*b*) had identical infrared spectra. In ultraviolet light the product in ethanol solution had a green fluorescence, and in benzene solution a blue fluorescence.

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[7] Edwards, Perkin, and Stoyle, *J.*, 1925, 195.

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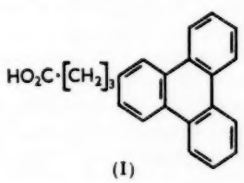
366. *A New Synthesis of Dibenz*[a,c]*anthracene, Benzo*[k]*fluoranthene, and Benzo*[b]*fluoranthene.*

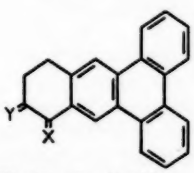
By NG. PH. BUU-HOÏ, DENISE LAVIT, and J. LAMY.

γ-2-Triphenylenylbutyric acid undergoes cyclisation at the 3-position, providing a new route to dibenz[*a*,*c*]anthracene, several of whose derivatives have also been prepared. Reaction of fluoranthene with succinic anhydride occurs predominantly at the 11-position, with some substitution at the 4-position. Cyclisation of γ-11-fluoranthenylbutyric acid takes place at the 12-position, and that of the 4-isomer at the 3-position, furnishing a new route to benzo[*k*]fluoranthene and benzo[*b*]fluoranthene.

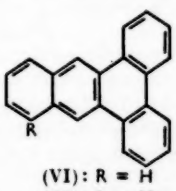
IN the Friedel–Crafts reaction with succinic anhydride, triphenylene reacts at the 2-position,[1] the resulting keto-acid being readily reduced to γ-2-triphenylenylbutyric acid (I). Cyclisation of the derived chloride has now been found to occur at the 3-position, giving



(I)



(II): X = O, Y = H_2
(III): X = Y = H_2
(IV): X = O, Y = CHPh
(V): X = O, Y = CH·$C_{10}H_7$

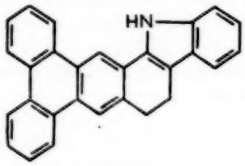


(VI): R = H
(VII): R = Me

10 : 11 : 12 : 13-tetrahydro-10-oxodibenz[*a*,*c*]anthracene (II), whose structure was established by Wolff–Kishner reduction and subsequent dehydrogenation by selenium to dibenz[*a*,*c*]anthracene (VI). The excellent yields recorded at each phase of this synthesis,

[1] Buu-Hoï and Jacquignon, *J.*, 1953, 941.

together with the ready availability of triphenylene, make the present method the most convenient one for the preparation of dibenz[*a,c*]anthracene, a hydrocarbon of biological interest for its reaction with skin proteins [2] in spite of its low carcinogenic activity.[3] A homologue, 10-methyldibenz[*a,c*]anthracene (VII), which can be considered as a derivative of the strongly carcinogenic 8-methylbenz[*a*]anthracene,[4] has also been prepared for biological testing, by selenium dehydrogenation of the crude product of the reaction of methylmagnesium iodide on the ketone (II). Alkali-catalysed condensation of the same



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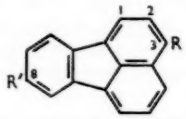
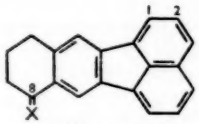


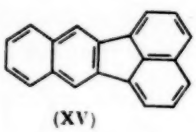
(IX): R = H, R′ = $CO\cdot[CH_2]_2\cdot CO_2H$
(X): R = H, R′ = $[CH_2]_3\cdot CO_2H$
(XI): R′ = H, R = $CO\cdot[CH_2]_2\cdot CO_2H$
(XII): R′ = H, R = $[CH_2]_3\cdot CO_2H$



(XIII): X = O
(XIV): X = H_2

ketone with benzaldehyde and α-naphthaldehyde readily afforded the arylidene-ketones (IV) and (V) which, surprisingly, resisted cyclodehydration with phosphoric oxide to the expected condensed fluorenes,[5] possibly because of too great steric strain in such hydrocarbons.[6] Supporting this explanation is the fact that the ketone (II) likewise failed to undergo a Pfitzinger reaction which would lead to a compound of molecular structure similar to those fluorenes, although its phenylhydrazone readily underwent the Fischer reaction, the resulting 5 : 6-dihydrotriphenylene[2,3-*a*]carbazole (VIII) having a more " symmetrical " structure.

Although the Friedel–Crafts reaction of fluoranthene with phthalic anhydride has often been investigated,[7] its reaction with succinic anhydride had not been reported. This reaction has now been found to give mostly γ-8-fluoranthenyl-γ-oxobutyric acid (IX) which was easily purified, although generally the products from Friedel–Crafts reactions with fluoranthene are difficult to isolate in the pure state.[8] The acid (IX) readily underwent Wolff–Kishner reduction to the acid (X), whose cyclisation took place in the 9-position



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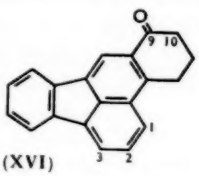
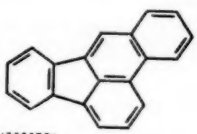


(XVI)



(XVII)

to give 8 : 9 : 10 : 11-tetrahydro-8-oxobenzo[*k*]fluoranthene (XIII); the structure of (XIII) was proved by its reduction to 8 : 9 : 10 : 11-tetrahydrobenzo[*k*]fluoranthene (XIV) followed by selenium dehydrogenation to benzo[*k*]fluoranthene (XV). This reaction

[1] Heidelberger *et al.*, *Cancer Res.*, 1951, **11**, 885; 1956, **16**, 442; *J. Amer. Chem. Soc.*, 1955, **77**, 2877; 1956, **78**, 3671.
[2] Cook, Hieger, Kennaway, and Mayneord, *Proc. Roy. Soc.*, 1932, *B*, **111**, 455.
[3] Barry, Cook, Haslewood, Hewett, Hieger, and Kennaway, *Proc. Roy. Soc.*, 1935, *B*, **117**, 318; Bachmann, Cook, Dansi, de Worms, Haslewood, Hewett, and Robinson, *ibid.*, 1937, *B*, **123**, 343.
[4] Cf. Rapson and Shuttleworth, *J.*, 1940, 636; Buu-Hoï and Cagniant, *Rev. sci.*, 1942, **80**, 319, 384, 436; 1943, **81**, 30; Saint-Ruf, Buu-Hoï, and Jacquignon, *J.*, 1958, 48.
[5] Cf. Buu-Hoï and Saint-Ruf, *J.*, 1957, 3806.
[6] von Braun and Manz, *Annalen*, 1932, **496**, 170; Campbell and Easton, *J.*, 1949, 341; Campbell, Leadill, and Wilshire, *J.*, 1951, 1404.
[7] Cf. D.R.-P. 624,918/1932; B.P. 468,648/1936.

sequence represents a convenient route to hydrocarbon (XV), already prepared by other methods.[9] Starting from the 3-fluoranthenyl acid (XI), obtained in very low yield as a by-product in the reaction of succinic anhydride with fluoranthene, the same reaction sequence led to benzo[*b*]fluoranthene (XVII), by way of the acid (XII) and 9 : 10 : 11 : 12-tetrahydro-9-oxobenzo[*b*]fluoranthene (XVI).

Experimental

Cyclisation of γ-2-Triphenylenylbutyric Acid.—This acid (11·5 g.) was prepared by refluxing for 4 hr. a solution of β-2-triphenylenoylpropionic acid (16 g.; m. p. 224°), 95% hydrazine hydrate (16 g.), and potassium hydroxide (15 g.) in diethylene glycol (250 c.c.); after cooling and dilution with water, the acid was precipitated on acidification with hydrochloric acid, and recrystallised from benzene. The m. p. (173°) is slightly above that previously recorded (168°). This acid (11·8 g.) was converted into its chloride by refluxing for 4 hr. its solution in ether (150 c.c.) with thionyl chloride (6·4 g.) and 6 drops of pyridine. The crude chloride obtained on evaporation of the solvent *in vacuo* was dissolved in anhydrous nitrobenzene (150 c.c.), and to the solution was added aluminium chloride (5·7 g.) in small portions with stirring, and the mixture left for 2 days at room temperature. After decomposition with ice, the solvent was steam-distilled, the brown solid residue was collected, washed with water, dried, and taken up in boiling ethanol (3000 c.c.), and the ethanolic solution was filtered. Concentration of the filtrate yielded, on cooling, 10 : 11 : 12 : 13-*tetrahydro*-10-*oxodibenz*[a,c]*anthracene* (II), which recrystallised from ethanol as cream-coloured needles (8·5 g.), giving an orange halochromy in sulphuric acid (Found: C, 89·0; H, 5·5. $C_{22}H_{16}O$ requires C, 89·2; H, 5·4%). An attempt to condense this ketone (1 g.) with isatin (0·6 g.) and potassium hydroxide (0·6 g.) in ethanol–dioxan (24 hours' refluxing) failed to furnish the corresponding cinchoninic acid.

10 : 11 : 12 : 13-*Tetrahydrodibenz*[a,c]*anthracene* (III).—A solution of the foregoing ketone (1 g.), hydrazine hydrate (1 g.), and potassium hydroxide (1 g.) in diethylene glycol (30 c.c.) was refluxed for 5 hr. and, after cooling, diluted with water; the solid precipitate was collected and recrystallised from *cyclo*hexane, giving needles (0·85 g.), m. p. 202° (Found: C, 93·5; H, 6·6. $C_{22}H_{18}$ requires C, 93·6; H, 6·4%). This hydrocarbon failed to give a picrate, and the yellow addition compound (m. p. 203°) with 1 : 3 : 5-trinitrobenzene was unstable on recrystallisation from ethanol.

Dibenz[a,c]*anthracene* (VI).—The foregoing tetrahydro-compound (0·75 g.) and selenium powder (0·75 g.) were heated at 350° for 2½ hr.; after cooling, the product was taken up in acetic acid (in which selenium is insoluble). A second crystallisation from the same solvent yielded colourless needles (0·4 g.), m. p. 205°, giving a picrate, m. p. 208° (lit.:[10] hydrocarbon, m. p. 205°; picrate, m. p. 207°.

11-*Benzylidene*-10 : 11 : 12 : 13-*tetrahydro*-10-*oxodibenz*[a,c]*anthracene* (IV).—A solution of ketone (II) (2 g.) and benzaldehyde (0·9 g.) in dioxan (50 c.c.) was mixed with a solution of potassium hydroxide (4 g.) in ethanol (45 c.c.) and refluxed for 10 min. After cooling, water was added, and the solid precipitate was washed with water, then with ethanol, dried, and recrystallised from ethanol–benzene, giving beige needles (2·5 g.), m. p. 225°, with a blood-red halochromy in sulphuric acid (Found: C, 90·3; H, 5·3. $C_{29}H_{20}O$ requires C, 90·6; H, 5·2%) In an attempt to cyclodehydrate this compound (2·3 g.) by refluxing for 26 hr. its solution in xylene (50 c.c.) with phosphoric oxide (1·7 g.), some of the ketone (1·1 g.) was recovered unchanged, along with a black insoluble residue.

10 : 11 : 12 : 13-*Tetrahydro*-11-α-*naphthylmethylene*-10-*oxodibenz*[a,c]*anthracene* (V).—Prepared as above from ketone (II) (2 g.) and α-naphthaldehyde (1·3 g.), this *ketone* crystallised as beige needles (2·9 g.), m. p. 194—195° (from ethanol–benzene), giving a violet halochromy in sulphuric acid (Found: C, 91·1; H, 5·2. $C_{33}H_{22}O$ requires C, 91·2; H, 5·1%).

10-*Methyldibenz*[a,c]*anthracene* (VII).—To a Grignard reagent prepared from magnesium (0·36 g.) and methyl iodide (2 g.) in ether (25 c.c.), a solution of ketone (II) (2 g.) in anhydrous benzene (120 c.c.) was added, and the mixture refluxed for 2 hr. After cooling, and decomposition with 10% aqueous sulphuric acid, more benzene was added, the organic solution washed with water and dried (Na_2SO_4), the solvent distilled, and the crystalline residue heated with

[9] Cf. Moureu, Chovin, and Pivod, *Compt. rend.*, 1946, **223**, 951; Campbell and Gow, *J.*, 1949, 1555; Orchin and Reggel, *J. Amer. Chem. Soc.*, 1947, **69**, 505.

[10] Cf. Clar, "Aromatische Kohlenwasserstoffe," Springer-Verlag, Berlin, 1952, p. 196.

selenium (2 g.) at 330° for 2 hr. Repeated recrystallisation of the product from benzene afforded needles (0·85 g.), m. p. 201°, which gave no halochromy in sulphuric acid (Found: C, 94·4; H, 5·8. $C_{23}H_{16}$ requires C, 94·5; H, 5·5%). The *picrate* formed dark red needles, m. p. 185°, from benzene (Found: N, 8·0. $C_{29}H_{19}O_7N_3$ requires N, 8·0%).

5 : 6-*Dihydrotriphenylene*[2,3-a]*carbazole* (VIII).—Ketone (II) (0·35 g.) was heated with phenylhydrazine (1 g.) at 140° for 5 min., and the crude yellow solid phenylhydrazone was treated with a saturated solution of hydrogen chloride in acetic acid (15 c.c.) for 1 hr. The precipitated *carbazole* was washed with water, dried, and recrystallised from toluene, giving beige prisms (0·3 g.), m. p. 282°, whose toluene solutions showed a blue fluorescence (Found: C, 90·7; H, 5·3. $C_{28}H_{19}N$ requires C, 91·0; H, 5·2%).

Reaction of Fluoranthene with Succinic Anhydride.—To a solution of fluoranthene (100 g.) and succinic anhydride (56 g.) in dry nitrobenzene (1500 c.c.), aluminium chloride (133 g.) was added in small portions with stirring, and the dark green mixture left at room temperature for 4 days. After decomposition with ice and steam-distillation of the solvent, a brown solid was obtained which, after several recrystallisations from acetic acid, yielded *γ-8-fluoranthenyl-γ-oxobutyric acid* (IX), yellow prisms (72 g.), m. p. 209°, giving an orange-red halochromy in sulphuric acid (Found: C, 79·6; H, 5·0. $C_{20}H_{14}O_3$ requires C, 79·5; H, 4·7%). Dilution of the mother-liquors with water gave a solid, m. p. 179—182°, which, after repeated recrystallisation from acetone, yielded *γ-3-fluoranthenyl-γ-oxobutyric acid* (XI), yellowish prisms (4·5 g.), m. p. 228° (Found: C, 79·2; H, 4·7%), giving a yellow-brown halochromy in sulphuric acid; the m. p. fell below 195° on admixture with a sample of the isomeric acid.

γ-8-Fluoranthenylbutyric Acid (X).—The foregoing keto-acid (79 g.), reduced in the usual way with hydrazine hydrate (100 g.) and potassium hydroxide (80 g.) in diethylene glycol (700 c.c.; 7 hr.), yielded an *acid*, crystallising as cream-coloured needles (68 g.), m. p. 135°, from benzene (Found: C, 83·3; H, 5·9. $C_{20}H_{16}O_2$ requires C, 83·3; H, 5·6%).

8 : 9 : 10 : 11-*Tetrahydro-8-oxobenzo*[k]*fluoranthene* (XIII).—The foregoing acid (67 g.) was converted into its chloride by refluxing for 3 hr. its solution in anhydrous ether (500 c.c.) with thionyl chloride (43 g.) and 20 drops of anhydrous pyridine; the crude acid chloride obtained on evaporation of the solvent *in vacuo* was dissolved in nitrobenzene (500 c.c.), and aluminium chloride (37 g.) was added in small portions with stirring. After 3 days at room temperature, the brown-yellow solution was decomposed with ice, the nitrobenzene steam-distilled, and the residue recrystallised from toluene, forming yellow leaflets (33 g.), m. p. 224°, giving a yellowish-brown halochromy in sulphuric acid (Found: C, 88·4; H, 5·2. $C_{20}H_{14}O$ requires C, 88·7; H, 5·2%).

8 : 9 : 10 : 11-*Tetrahydrobenzo*[k]*fluoranthene* (XIV).—The above ketone (3 g.) was heated at 110—120° with hydrazine hydrate (3 g.) in diethylene glycol (100 c.c.) until dissolution occurred; potassium hydroxide (3 g.) was then added, and the mixture was refluxed for 5 hr. After cooling and dilution with water, the yellow precipitate was collected, washed with water, and recrystallised from ethanol, giving yellow needles (2·25 g.), m. p. 122° (Found: C, 93·6; H, 6·3. $C_{20}H_{16}$ requires C, 93·7; H, 6·3%).

Benzo[k]*fluoranthene* (XV).—A mixture of the above tetrahydro-compound (1·3 g.) and selenium (1 g.) was heated at 340° for 3 hr. and, after cooling, the product was collected and recrystallised twice from acetic acid, giving yellowish prisms (1·1 g.), m. p. 217°, identical with the hydrocarbon synthesised by Moureu, Chovin, and Pivod's method.[9] Its solutions in acetic acid showed an intense blue fluorescence.

γ-3-Fluoranthenylbutyric Acid (XII).—Wolff–Kishner reduction of 3-γ-fluoranthenyl-γ-oxobutyric acid (2·7 g.) furnished an *acid*, crystallising as cream-coloured prisms (1·8 g.), m. p. 141°, from benzene (Found: C, 83·2; H, 5·8. $C_{20}H_{16}O_2$ requires C, 83·3; H, 5·6%).

9 : 10 : 11 : 12-*Tetrahydro-9-oxobenzo*[b]*fluoranthene* (XVI).—The foregoing acid (1·5 g.) was cyclised as for the homologue (X); the cyclic *ketone* (XVI) obtained formed cream-coloured needles (0·9 g.), m. p. 150—151° (from ethanol), giving a yellowish-brown halochromy in sulphuric acid (Found: C, 88·1; H, 5·4. $C_{20}H_{14}O$ requires C, 88·7; H, 5·2%).

Benzo[b]*fluoranthene* (XVII).—Wolff–Kishner reduction of the foregoing ketone (0·8 g.) with hydrazine hydrate (1 c.c.) and potassium hydroxide (1 g.) afforded a viscous oily hydrocarbon which failed to crystallise and was characterised by its picrate, orange needles, m. p. 169° (from ethanol). This crude oil (0·45 g.) was dehydrogenated by 3 hours' heating with selenium (0·4 g.) at 350°, and the product was taken up in benzene; after evaporation of the solvent, the residue was recrystallised from ethanol (100 c.c.), giving *benzo*[b]*fluoranthene* as

almost colourless needles (0·35 g.), m. p. 168° (Found: C, 95·2; H, 4·8. Calc. for $C_{20}H_{12}$: C, 95·2; H, 4·8%). The picrate formed yellow needles, m. p. 156°, from ethanol, and the addition product with 1 : 3 : 5-trinitrobenzene formed orange-yellow needles, m. p. 179°, from ethanol. This hydrocarbon was isolated from coal-tar pitch by Kruber and Oberkobusch,[11] who gave m. p. 168°, and m. p. 155—156° for the picrate.

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THE RADIUM INSTITUTE, THE UNIVERSITY OF PARIS. [*Received, December 10th,* 1958.]

[11] Kruber and Oberkobusch, *Chem. Ber.*, 1952, **85**, 433.

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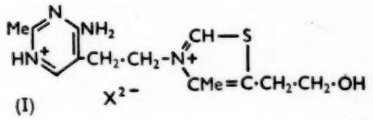
367. *Two Isomeric Homologues of Thiamine.*

By J. BIGGS and P. SYKES.

The synthesis of two isomeric homologues of thiamine is described, and their behaviour with alkali, potassium ferricyanide, and deuterium oxide and as catalysts for the conversion of pyruvate + acetaldehyde into acetoin + carbon dioxide is reported.

IN a study of the behaviour of quaternary thiazolium compounds as catalysts for the conversion of pyruvate + acetaldehyde into acetoin + CO_2,[1] compounds having desirable features were the isomeric thiamine homologues (I; X = $2Cl^-$) and (II).

The essential intermediate for our synthesis of compound (I) was the amine (III; R = NH_2, R′ = $CH_2{\cdot}NH_2$). This is mentioned in a patent [2] but we were unable to repeat the reactions there outlined. We failed also in attempts to obtain the amine from readily available thiamine derivatives, *e.g.*, through the cyanide (III; R = NH_2, R′ = CN) [obtainable by dehydration of the amide (III; R = NH_2, R′ = $CO{\cdot}NH_2$) or from the bromide (III; R = NH_2, R′ = Br) and potassium cyanide], and by reduction of the amide (III; R = NH_2, R′ = $CO{\cdot}NH_2$).



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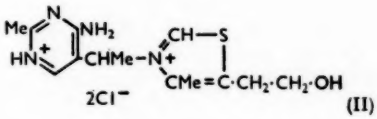

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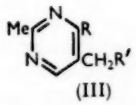

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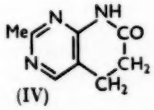

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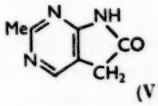


(V)

Condensation of acetamidine with dimethyl α-formylglutarate followed by cyclisation with acid yielded the hydroxy-ester (III; R = OH, R′ = $CH_2{\cdot}CO_2Me$), which with phosphorus oxychloride gave the chloro-ester (III; R = Cl, R′ = $CH_2{\cdot}CO_2Me$); but with methanolic ammonia at 110°, this chloro-ester was converted, not into the expected amino-amide (III; R = NH_2, R′ = $CH_2{\cdot}CO{\cdot}NH_2$), but into the cyclic lactam (IV). To ensure that this cyclisation was not due to over-vigorous reaction conditions, the chloro-ester was stirred with aqueous ammonia at room temperature, but only the amino-acid (III; R = NH_2, R′ = $CH_2{\cdot}CO_2H$) could be obtained. No attempt was made to prepare the desired amide by esterification and ammonolysis of this amino-acid, in the light of our previous experience of the spontaneous cyclisation of the esters of other pyrimidine amino-acids.[3]

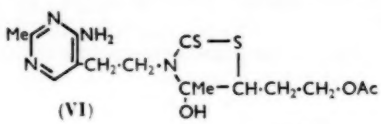
[1] Downes and Sykes, *Chem. and Ind.*, 1957, 1095.
[2] U.S.P. 2,377,395.
[3] Nesbitt and Sykes, *J.*, 1954, 3057.

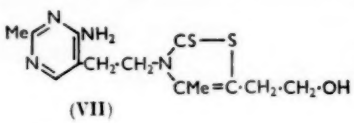
Refluxing the lactam (IV) with 100% hydrazine hydrate, however, led to the hydrazide (III; R = NH_2, R′ = CH_2·CO·NH·NH_2). An acid solution of this compound was then treated with sodium nitrite, and the solution containing the azide (III; R = NH_2, R′ = CH_2·CO·N_3) heated until no more nitrogen was evolved, but basification followed by freeze-drying and vacuum-sublimation gave the lactam (IV) as the only product. This acylation of the 4-amino-group of the pyrimidine nucleus by the azide first formed was somewhat surprising in the face of the weakly basic nature of this amino-group. However, it appears to be a general reaction of suitable 4-aminopyrimidines, for on similar treatment of 4-amino-2-methyl-5-pyrimidylacethydrazide [3] (III; R = NH_2, R′ = CO·NH·NH_2), a lactam (V) with a 5-membered ring was obtained, though the corresponding 4-hydroxy-compound (III; R = OH, R′ = CO·NH·NH_2) yields the expected amine (III; R = OH, R′ = NH_2) in the normal way.[4]

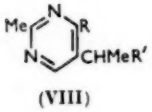
If, however, the treatment with sodium nitrite was carried out in the presence of a large excess of acid, protonation of the amino-pyrimidine system protected the 4-amino-group, and the desired amine (III; R = NH_2, R′ = CH_2·NH_2) was then obtained. Treating [5] the amine with carbon disulphide, ammonia, and 5-acetoxy-3-chloropentan-2-one yielded the expected [6] 4-hydroxythiazolid-2-thione (VI) which underwent acid-catalysed dehydration to the thiazolin-2-thione (VII).

Hydrogen peroxide oxidised the thiazoline (VII) to the thiazolium sulphate (I; X = SO_4^{2-}), which with barium chloride yielded the desired chloride hydrochloride (I; X = $2Cl^-$).

In the synthesis of the second analogue an amine (VIII; R′ = NH_2) was needed. Condensing acetamidine with dimethyl α-formyl-β-methylsuccinate yielded the hydroxy-ester (VIII; R = OH, R′ = CO_2Me), a reaction extremely sensitive to the amount of sodium ethoxide used as catalyst and to the time of heating; diethyl α-formyl-β-methyl-succinate was rather more sensitive than the corresponding dimethyl ester which also


(VI)


(VII)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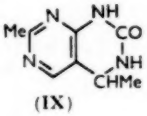
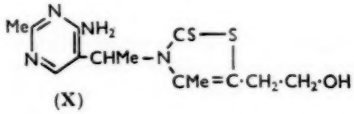

(IX)


(X)

condensed in better yield. The hydrochloride of the 4-hydroxypyrimidine methyl ester was, however, extremely susceptible to ester exchange so it is readily converted into the corresponding ethyl ester if desired. The latter was then converted into the chloro-compound (VIII; R = Cl, R′ = CO_2Et), which with methanolic ammonia, in contrast to the previous series, yielded the expected amide (VIII; R = NH_2, R′ = CO·NH_2). But this, on reaction with sodium hypobromite by the method of Hoogewerff and van Dorp,[7] was converted, not into the expected amine, but into the ring compound (IX) by attack of the intermediate *iso*cyanate (VIII; R = NH_2, R′ = NCO) on the pyrimidine 4-amino-group, the yield being almost quantitative. This reaction was most unexpected as Gravin [8] was able to convert 4-amino-2-methyl-5-pyrimidylacetamide (III; R = NH_2, R′ = CO·NH_2) into the corresponding amine (III; R = R′ = NH_2) in reasonable yield. The cyclic urea (IX) could not be hydrolysed to the desired amine.

[4] Cerecedo and Pickel, *J. Amer. Chem. Soc.*, 1937, **59**, 1714.
[5] Sykes and Todd, *J.*, 1951, 534.
[6] Sykes, *J.*, 1955, 2390.
[7] Hoogewerff and van Dorp, *Rec. Trav. chim.*, 1887, **6**, 373.
[8] Gravin, *J. Appl. Chem.* (*U.S.S.R.*), 1943, **16**, 105.

The amide was, therefore, converted into the hydrazide (VIII; R = NH_2, R′ = CO·NH·NH_2) but on treatment with sodium nitrite in highly acid solution this yielded, not, as in the previous series, the desired amine, but the cyclic urea (IX). Reaction of the hydrazide with hydrogen chloride and pentyl nitrite in dry ethanol, however, yielded the ethylurethane (VIII; R = NH_2, R′ = NH·CO_2Et). This has the nitrogen atom in the desired position but unfortunately proved extremely resistant to hydrolysis with acid or alkali and it was impossible to remove the ethoxycarbonyl group without further decomposition. The corresponding benzylurethane (VIII; R = NH_2, R′ = NH·CO_2·CH_2Ph) was therefore prepared; this was smoothly hydrogenolysed to the desired amine (VIII; R = R′ = NH_2). This most satisfactory overall reaction from hydrazide to amine was equally successful in the synthesis of the first homologue.

Treatment of the amine (VIII; R = R′ = NH_2) with carbon disulphide and 5-acetoxy-3-chloropentan-2-one, followed by acid-catalysed dehydration, yielded the thiazolin-2-thione (X) and thence as above the thiamine homologue (II).

Adding alkali to an aqueous solution of a salt (I) does not give a yellow colour, as thiamine does, nor does adding potassium ferricyanide to this solution produce thiochrome-like fluorescence. By contrast, the analogue (II) did give a yellow colour with alkali, and ferricyanide oxidation then produced a bright blue fluorescence. These observations are in accord with our views on the action of oxidising agents on thiamine itself.[5,9]

On treatment with one equivalent of alkali (to convert them into the quaternary chlorides) in deuterium oxide both homologues exchanged the hydrogen atom at $C_{(2)}$ of the thiazolium nucleus for deuterium virtually instantaneously; the exchange was followed and confirmed by nuclear magnetic resonance and infrared spectral measurements.[10] The speed of exchange was identical with that of thiamine under similar conditions.[11] Both the homologues acted as catalysts in the non-enzymic conversion, pyruvate + acetaldehyde ⟶ acetoin + CO_2,[12,13] compound (I) showing 67%, and compound (II) 5%, of the activity of thiamine under similar conditions. Neither homologue showed vitamin activity in a microbiological test with *Kloeckera brevis*.

Experimental

Dimethyl α-Formylglutarate.—Dimethyl glutarate (100·5 g.), ethyl formate (90 g., 1·92 mol.), sodium wire (24·8 g., 1·72 g.-atom), and dry ether (500 ml.) were heated under reflux for 4 hr., then kept overnight. All the sodium had then dissolved and a viscous red sodio-derivative separated. The ether layer was decanted, washed with water (50 ml.), dried (Na_2SO_4), and distilled under reduced pressure, yielding dimethyl glutarate (44·9 g.). The red sodio-derivative was dissolved in water, the aqueous washings of the ethereal layer were added, and the solution was acidified with dilute sulphuric acid and extracted repeatedly with ether. The ethereal extract was dried (Na_2SO_4) and distilled, yielding 46·4 g. (40%) of the formyl ester, b. p. 100—101°/0·1 mm. Formylation of diethyl glutarate yielded *diethyl α-formylglutarate* (36%), b. p. 129°/3 mm. (Found: C, 55·2; H, 7·1. $C_{10}H_{16}O_5$ requires C, 55·4; H, 7·4%).

Methyl β-(4-Hydroxy-2-methyl-5-pyrimidyl)propionate (III; R = OH, R′ = CH_2·CO_2Me).—Acetamidine hydrochloride (36·6 g.) was added to a solution of sodium (8·8 g., 1 g.-atom) in ethanol (900 ml.), and the precipitated sodium chloride removed on a centrifuge. Dimethyl α-formylglutarate (72·2 g., 1 mol.) was added to the filtrate and the solution heated under reflux for 3 hr., cooled, treated with dry hydrogen chloride until no more sodium chloride separated, filtered (" Hyflo Supercel "), and further treated with hydrogen chloride until crystals began to separate (further material was obtained by saturating the original mother-liquors with hydrogen chloride and storing the solution). Recrystallising the *hydroxy-ester hydrochloride* from ethanol gave 41·7 g. (47%) of colourless needles, m. p. 223° (Found: C, 46·4; H, 5·6; N, 12·1. $C_9H_{13}O_3N_2Cl$ requires C, 46·5; H, 5·7; N, 12·1%).

[9] Nesbitt and Sykes, *J.*, 1954, 4585.
[10] Breslow, *J. Amer. Chem. Soc.*, 1957, **79**, 1762.
[11] Sykes and Downes, unpublished work.
[12] Mizuhara, Tamura, and Arata, *Proc. Japan Acad.*, 1951, **27**, 302.
[13] Mizuhara and Handler, *J. Amer. Chem. Soc.*, 1954, **76**, 571.

Treating an aqueous solution of the hydrochloride with sodium hydrogen carbonate, followed by freeze-drying and sublimation at 110°/10^{-4} mm., yields the free *base*, m. p. 109° (Found: C, 55·1; H, 6·4; N, 14·4. $C_9H_{12}O_3N_2$ requires C, 55·1; H, 6·2; N, 14·3%).

Similar treatment of diethyl α-formylglutarate yields *ethyl* β-(*4-hydroxy-2-methyl-5-pyrimidyl*)-*propionate hydrochloride*, m. p. 221—222° (Found: C, 48·7; H, 6·1; N, 11·6. $C_{10}H_{15}O_3N_2Cl$ requires C, 48·7; H, 6·1; N, 11·4%), which is converted by alkali into the *base*, m. p. 113° (Found: C, 56·9; H, 7·0; N, 13·6. $C_{10}H_{14}O_3N_2$ requires C, 57·2; H, 6·7; N, 13·3%).

Methyl β-(*4-Chloro-2-methyl-5-pyrimidyl*)*propionate* (III; R = Cl, R′ = CH_2·CO_2Me).—Methyl 4-hydroxy-2-methyl-5-pyrimidylpropionate (12 g.) was powdered and added to redistilled phosphorus oxychloride (200 ml.), and the mixture was heated under reflux. All solid dissolved in 10 min. and heating was continued for a further 30 min. The excess of phosphorus oxychloride was then removed under reduced pressure, and the flask then rotated so that the product spread as a thin layer over its surface. The flask was then cooled in ice-water, and the viscous product dissolved in ice-water, brought to pH 8, and extracted repeatedly with ether. The extract was dried (Na_2SO_4), the solvent removed, and the residue distilled, yielding the *chloro-ester* (8·7 g., 78%), b. p. 134°/2·4 mm. (Found: C, 50·6; H, 5·3; N, 13·3. $C_9H_{11}O_2N_2Cl$ requires C, 50·4; H, 5·2; N, 13·1%). With phosphorus oxychloride the ethyl hydroxy-ester yielded the ethyl chloro-ester (68%), b. p. 105—108°/0·4 mm.

The oily methyl chloro-ester with hot 100% hydrazine hydrate yielded needles of the *hydrazide* (III; R = NH·NH_2, R′ = CH_2·CO·NH·NH_2), m. p. 182° (Found: C, 46·0; H, 6·9; N, 40·0. $C_8H_{14}ON_6$ requires C, 45·7; H, 6·7; N, 40·0%).

Action of Ammonia on Methyl β-(*4-Chloro-2-methyl-5-pyrimidyl*)*propionate*.—(*a*) The above chloro-ester (0·6 g.) was stirred with ammonia solution (*d* 0·880; 150 ml.) until dissolved (4 hr.). The solution was left overnight, then concentrated under reduced pressure to 5 ml. Ethanol (20 ml.) was added, and the solution cooled in ice; crystals separated which were collected and sublimed at 190°/10^{-4} mm., to yield β-(*4-amino-2-methyl-5-pyrimidyl*)*propionic acid* (III; R = NH_2, R′ = CH_2·CO_2H), m. p. 233° (Found: C, 52·8; H, 6·1; N, 23·4. $C_8H_{11}O_2N_3$ requires C, 52·7; H, 6·1; N, 23·1%).

(*b*) The chloro-ester (4·2 g.) was heated in an autoclave with saturated methanolic ammonia (70 ml.) at 90—100° for 7 hr. The solution, from which some solid had separated, was evaporated to dryness under reduced pressure and the residue recrystallised (charcoal) from ethanol containing a little water, to yield 5 : 6 : 7 : 8-*tetrahydro-2-methyl-7-oxo*-1 : 3 : 8-*triazanaphthalene* (IV) (1·83 g., 57%) as colourless plates, m. p. 256° (Found: C, 58·9; H, 5·3; N, 26·0. $C_8H_9ON_3$ requires C, 58·9; H, 5·5; N, 25·8%).

4-Amino-2-methyl-5-pyrimidylpropionhydrazide (III; R = NH_2, R′ = CH_2·CO·NH·NH_2).—The cyclic compound (IV) (0·88 g.) was heated under reflux in 100% hydrazine hydrate (20 ml.) for 45 min. On cooling, a mass of crystals separated. Recrystallisation from dry ethanol affords the *hydrazide* (0·84 g., 80%) as colourless needles, m. p. 201° (Found: C, 49·1; H, 6·5; N, 36·1. $C_8H_{13}ON_5$ requires C, 49·2; H, 6·7; N, 35·8%).

4-Amino-5-2′-aminoethyl-2-methylpyrimidine (III; R = NH_2, R′ = CH_2·NH_2).—The preceding hydrazide (0·20 g.) was dissolved in 3N-hydrochloric acid (4·5 ml., 12 mol.), then cooled to −2°, and a solution of sodium nitrite (0·075 g., 1·06 mol.) slowly added with stirring. After a further 15 min. the solution was warmed to 60° (nitrogen was evolved), brought to pH 8·9 and freeze-dried. Three sublimations at 120°/10^{-4} mm. yielded the *amine* (0·064 g., 41%), m. p. 101° (Found: C, 55·0; H, 7·8; N, 36·5. $C_7H_{12}N_4$ requires C, 55·3; H, 8·0; N, 36·8%).

The action of nitrous acid on the hydrazide under a wide variety of other conditions yielded varying quantities of the cyclic lactam (IV), but no amine on sublimation of the freeze-dried reaction mixtures.

5-2′-Acetoxyethyl-3-2′-(*4-amino-2-methyl-5-pyrimidyl*)*ethyl-4-hydroxy-4-methylthiazolid-2-thione* (VI).—The hydrazide (1·20 g.) was treated with nitrous acid as above, and the solution made alkaline, evaporated to dryness under reduced pressure and extracted with ethanol (4 × 20 ml.). The ethanol extract was concentrated (3 ml.) and to it were added water (1·5 ml.), ammonia solution (*d* 0·880; 0·26 g.), and carbon disulphide (0·30 g.). The mixture was shaken until all the carbon disulphide had dissolved, 5-acetoxy-3-chloropentan-2-one (0·54 g.) was then added, and the whole shaken for 1 hr. and left overnight. Solid separated which on recrystallisation from aqueous ethanol yielded the thiazolid-2-thione (0·172 g., 7·5% calc. on hydrazide), m. p. 258°.

3-2′-(*4-Amino-2-methyl-5-pyrimidyl*)*ethyl-5-2′-hydroxyethyl-4-methylthiazolin-2-thione* (VII).—

The above thiazolid-2-thione (0·3 g.) was dissolved in 3N-hydrochloric acid (3 ml.) and heated just to the b. p., then cooled and made just alkaline. Recrystallisation of the separated material from methanol yielded the *thiazolin-2-thione* (0·1 g., 34%), m. p. 230° (Found: C, 50·7; H, 5·9; N, 18·3. $C_{13}H_{18}ON_4S_2$ requires C, 50·3; H, 5·8; N, 18·1%).

3-2′-(4-Amino-2-methyl-5-pyrimidyl)ethyl-5-2′-hydroxyethyl-4-methylthiazolium Sulphate (I; X = SO_4^{2-}).—The above thiazolin-2-thione (0·071 g.) was suspended in water (1·4 ml.), 30% hydrogen peroxide (0·081 g., 3 mol.) added, and the mixture left with occasional shaking until all the solid had dissolved (2 hr.). It was then concentrated (0·5 ml.); ethanol (5 ml.) and acetone (20 ml.) were added. Crystals separated at 0° which were collected and washed with acetone. Recrystallisation from water–ethanol–acetone yielded the *sulphate* (I; X = SO_4^{2-}) (0·075 g., 87%) as colourless needles, m. p. 221° (decomp.) (Found: C, 37·7; H, 6·3; N, 13·9. $C_{13}H_{20}O_5N_4S_2,2H_2O$ requires C, 37·8; H, 5·9; N, 13·6%). Treatment of the aqueous solution with aqueous picric acid, followed by recrystallisation of the product from ethanol, yielded the *picrate*, m. p. 161° (decomp.) (Found: C, 40·7; H, 3·3; N, 19·3. $C_{25}H_{24}O_{15}N_{10}S$ requires C, 40·7; H, 3·3; N, 19·0%). Treating the aqueous solution of the sulphate with barium chloride solution, removing the barium sulphate on a centrifuge, concentrating the solution, and treating it as above yielded the *chloride hydrochloride* (I; X = $2Cl^-$) as needles, m. p. 257° (decomp.) (Found: C, 42·1; H, 6·1; N, 15·0. $C_{13}H_{20}ON_4Cl_2S,H_2O$ requires C, 42·3; H, 6·3; N, 15·2%).

Dimethyl α-Formyl-β-methylsuccinate.—Dimethyl α-methylsuccinate (189·5 g.), ethyl formate (dried over K_2CO_3; 175 g., 2 mol.), sodium wire (27·2 g., 1 g.-atom), and dry ether (1420 ml.) were left at room temperature for 24 hr., then worked up as described for dimethyl α-formylglutarate. Dimethyl α-methylsuccinate (98·8 g.) was recovered, and the formyl ester (77·2 g., 34%) distilled (b. p. 100°/1 mm.). Similar formylation of diethyl α-methylsuccinate yielded the corresponding diethyl formyl ester [14] (53%), b. p. 114°/0·3 mm.

Methyl α-(4-Hydroxy-2-methyl-5-pyrimidyl)propionate (VIII; R = OH, R′ = CO_2Me).—Acetamidine hydrochloride (65 g., 1·3 mol.) was stirred with a solution of sodium (16·5 g., 1·35 g.-atom) in ethanol (400 ml.) for 15 min., and the separated sodium chloride removed on a centrifuge. Dimethyl α-formyl-β-methylsuccinate (99·2 g., 1 mol.) was added to the filtrate, and the deep red solution heated under reflux for 2 hr. The cooled solution was then treated with dry hydrogen chloride, the trace of separated sodium chloride removed, and the volume reduced to 200 ml. On cooling to 0°, crystals separated. More product was obtained by further concentration until acetamidine hydrochloride (m. p. 167°) began to be deposited. Recrystallisation from ethanol yielded the *hydroxy-ester hydrochloride* (61·7 g., 51%) as colourless needles, m. p. 205° (Found: C, 46·9; H, 5·7; N, 12·0. $C_9H_{13}O_3N_2Cl$ requires C, 46·5; H, 5·7; N, 12·1%). Similar treatment of diethyl α-formyl-β-methylsuccinate yields *ethyl α-(4-hydroxy-2-methyl-5-pyrimidyl)propionate hydrochloride* (37%), m. p. 211° (Found: C, 48·4; H, 5·9; N, 11·2. $C_{10}H_{15}O_3N_2Cl$ requires C, 48·7; H, 6·1; N, 11·4%), and the corresponding free *base*, m. p. 124° (Found: C, 57·0; H, 6·9; N, 13·4. $C_{10}H_{14}O_3N_2$ requires C, 57·1; H, 6·7; N, 13·3%).

Ethyl α-(4-Chloro-2-methyl-5-pyrimidyl)propionate (VIII; R = Cl, R′ = CO_2Et).—Powdered ethyl α-(4-hydroxy-2-methyl-5-pyrimidyl)propionate hydrochloride (27 g.) was heated with redistilled phosphorus oxychloride (250 ml.) for 20 min.; this yielded the *chloro-ester* (14·6 g., 59%), b. p. 99—100°/0·05 mm. (Found: C, 52·8; H, 6·0; N, 11·9. $C_{10}H_{13}O_2N_2Cl$ requires C, 52·6; H, 5·7; N, 12·2%).

α-(4-Amino-2-methyl-5-pyrimidyl)propionamide (VIII; R = NH_2, R′ = CO·NH_2).—The above chloro-ester (18 g.) was heated in an autoclave with saturated methanolic ammonia (140 ml.) at 110—120° for 10 hr. The mixture of solid and red solution was evaporated to dryness and the residue recrystallised from water (charcoal), to yield the *amino-amide* (9·2 g., 61%) as colourless needles, m. p. 231° (Found: C, 53·2; H, 6·2; N, 30·9. $C_9H_{12}ON_4$ requires C, 53·3; H, 6·6; N, 31·1%).

Action of Hypobromite on α-(4-Amino-2-methyl-5-pyrimidyl)propionamide.—The amide (0·592 g.) was dissolved in hot water (25 ml.), and the solution cooled to 0° and treated with sodium hypobromite (1·1 mol.) made from sodium hydroxide (0·78 g.) in water (4·5 ml.) to which bromine (0·19 ml.) was added. After 10 min. the temperature was raised to 80° and maintained for a further 20 min. Dilute sulphuric acid was then added to the cooled solution until the pH was 7. Crystals separated which, on recrystallisation from aqueous methanol, yielded *1 : 2 : 3 : 4-tetrahydro-4 : 7-dimethyl-2-oxo-1 : 3 : 6 : 8-tetra-azanaphthalene* (IX) (0·58 g.,

[14] Fichter and Rudin, *Ber.*, 1904, **37**, 1611.

99%) as colourless prisms, m. p. 312° (decomp.) (Found: C, 53·9; H, 5·6; N, 31·4. $C_8H_{10}ON_4$ requires C, 53·8; H, 5·6; N, 31·4%).

α-(4-Amino-2-methyl-5-pyrimidyl)propionhydrazide (VIII; R = NH_2, R′ = $CO{\cdot}NH{\cdot}NH_2$).—The amide (1·03 g.) was heated in 100% hydrazine hydrate (7 ml.) under reflux for 1·5 hr.; on cooling, a mass of crystals separated. Recrystallisation from ethanol affords the *hydrazide* (1·01 g., 90%) as colourless needles, m. p. 263° (Found: C, 48·9; H, 7·0; N, 35·5. $C_8H_{13}ON_5$ requires C, 49·2; H, 6·7; N, 35·8%).

Action of Nitrous Acid on α-(4-Amino-2-methyl-5-pyrimidyl)propionhydrazide.—The hydrazide (0·216 g.) in 3N-hydrochloric acid (4·5 ml., 12 mol.) was treated at −2° with a solution of sodium nitrite (0·113 g., 1·06 mol. dropwise with continual shaking. After 15 min., the temperature was raised to 60° and maintained until no more nitrogen was evolved. Sodium hydrogen carbonate was added to give pH 8·3, causing the separation of solid, m. p. and mixed m. p. 312° (decomp.) with the cyclic urea (IX).

Action of Nitrous Acid on 4-Amino-2-methyl-5-pyrimidylacethydrazide [3] (III; R = NH_2, R′ = $CO{\cdot}NH{\cdot}NH_2$).—Similar treatment of this hydrazide, followed by freeze-drying of the basified solution and sublimation at 140°/10^{-3} mm. yielded *6-methyl-1 : 5 : 7-triazaindan-2-one* (V), m. p. 220° (decomp.) (Found: C, 56·0; H, 5·2; N, 28·0. $C_7H_7ON_3$ requires C, 56·4; H, 4·8; N, 28·2%).

4-Amino-5-1′-ethoxycarbonylaminoethyl-2-methylpyrimidine (VIII; R = NH_2, R′ = $NH{\cdot}CO_2Et$).—A solution of the hydrazide (1·43 g.) in dry ethanol (190 ml.) containing dry hydrogen chloride (0·70 g., 2·2 mol.) and pentyl nitrite (1·24 g., 1·42 mol.; freshly distilled) was heated at 60° for 4 hr. The solvent was then removed, the residue dissolved in water (5 ml.), and the solution made just alkaline with sodium hydrogen carbonate. Solid separated which on recrystallisation from water (charcoal) yielded the *ethylurethane* (1·05 g., 64%) as colourless needles, m. p. 192° (Found: C, 53·7; H, 7·4; N, 24·9. $C_{10}H_{16}O_2N_4$ requires C, 53·6; H, 7·2; N, 25·0%).

4-Amino-5-1′-benzyloxycarbonylaminoethyl-2-methylpyrimidine (VIII; R = NH_2, R′ = $NH{\cdot}CO_2{\cdot}CH_2Ph$).—A solution of the hydrazide (0·60 g.) in benzyl alcohol (45 ml.; freshly distilled) containing dry hydrogen chloride (0·38 g., 2·2 mol.) and pentyl nitrite (0·43 g., 1·1 mol.; freshly distilled) was heated at 60° for 3 hr., the solution becoming yellow. The solvent was removed under reduced pressure and the oily residue dissolved in a mixture of ether and water. The aqueous layer was separated and extracted twice more with ether to remove benzyl alcohol. When the aqueous solution was made alkaline, the *benzylurethane* separated. Recrystallisation from water yielded colourless needles (0·45 g., 54%), m. p. 174° (Found: C, 62·8; H, 6·3; N, 19·6. $C_{15}H_{18}O_2N_4$ requires C, 62·9; H, 6·3; N, 19·6%).

4-Amino-5-2′-benzyloxycarbonylaminoethyl-2-methylpyrimidine (III; R = NH_2, R′ = $CH_2{\cdot}NH{\cdot}CO_2{\cdot}CH_2Ph$).—Similar treatment of 4-amino-2-methyl-5-pyrimidylpropionhydrazide (III; R = NH_2, R′ = $CH_2{\cdot}CO{\cdot}NH{\cdot}NH_2$) yielded the corresponding *benzylurethane* (65%) as needles, m. p. 142° (Found: C, 62·8; H, 6·1; N, 19·8. $C_{15}H_{18}O_2N_4$ requires C, 62·9; H, 6·3; N, 19·6%).

4-Amino-5-1′-aminoethyl-2-methylpyrimidine (VIII; R = R′ = NH_2).—A solution of the benzylurethane (0·225 g.) in ethanol (40 ml.) containing palladium black (0·07 g.) was stirred vigorously while hydrogen (carbon dioxide-free) was passed through until no more carbon dioxide was evolved (3 hr.). The solvent was removed under reduced pressure. The oily residue gradually crystallised. Sublimation (twice) at 100°/10^{-4} mm. yielded the *amine*, m. p. 103° (Found: C, 55·2; H, 8·1. $C_7H_{12}N_4$ requires C, 55·3; H, 8·0%).

The amine was characterised by reaction in aqueous solution with sodium dithioformate, the separated material being recrystallised from water to yield the *thioformyl derivative* (53%) as colourless prisms, m. p. 200° (decomp.) (Found: C, 49·3; H, 6·1; N, 28·5. $C_8H_{12}N_4S$ requires C, 49·0; H, 6·2; N, 28·6%).

4-Amino-5-2′-thioformylaminoethyl-2-methylpyrimidine (III; R = NH_2, R′ = $CH_2{\cdot}NH{\cdot}CHS$).—Similar hydrogenolysis of 4-amino-5-2′-benzyloxycarbonylaminoethyl-2-methylpyrimidine (III; R = NH_2, R′ = $CH_2{\cdot}NH{\cdot}CO_2{\cdot}CH_2Ph$) yielded the corresponding amine, characterised as its *thioformyl derivative* (56%), buff-coloured prisms, m. p. 197° (decomp.) (from water) (Found: C, 49·3; H, 6·3; N, 28·5. $C_8H_{12}N_4S$ requires C, 49·0; H, 6·2; N, 28·6%).

3-1′-(4-Amino-2-methyl-5-pyrimidyl)ethyl-5-2′-hydroxy)ethyl-4-methylthiazolin-2-thione (X).—The benzylurethane (4·35 g.) was hydrogenolysed as above, and the final aqueous solution evaporated to dryness. The residue was dissolved in water (4 ml.) and ethanol (10 ml.), ammonia

solution (*d* 0·880; 1·28 g.) and carbon disulphide (1·44 g.) then being added. The mixture was shaken until all the carbon disulphide had dissolved, 5-acetoxy-3-chloropentan-2-one (2·7 g.) was then added, and the mixture shaken vigorously for 3 hr. Next morning the mixture was evaporated to dryness under reduced pressure, and the residue taken up in 3N-hydrochloric acid (10 ml.), heated just to the b. p., allowed to cool slowly, and made just alkaline. Solid separated which on recrystallisation from aqueous methanol yielded the *thiazolin-2-thione* (2·23 g., 47%) as colourless needles, m. p. 230° (Found: C, 50·1; H, 6·0; N, 18·0. $C_{13}H_{18}ON_4S_2$ requires C, 50·3; H, 5·8; N, 18·1%).

3-1′-(4-*Amino*-2-*methyl*-5-*pyrimidyl*)*ethyl*-5-2′-*hydroxyethyl*-4-*methylthiazolium Chloride Hydrochloride* (II).—The thiazolin-2-thione (0·95 g.), water (30 ml.), and 24% hydrogen peroxide solution (1·26 g., 3 mol.) were stirred until the solid had dissolved (3 hr.), then treated with barium chloride solution until no more solid precipitated. The barium sulphate was removed on a centrifuge, and the solution evaporated to dryness. The residue was dissolved in methanol (20 ml.), and ether (30 ml.) added. The quaternary *chloride hydrochloride* (0·76 g., 70%) separated as needles, m. p. 177° (decomp.) (Found: C, 42·6; H, 6·2; N, 15·2. $C_{13}H_{20}ON_4Cl_2,H_2O$ requires C, 42·3; H, 6·3; N, 15·2%). Treatment of the aqueous solution with aqueous picric acid yields the *picrate* as yellow needles, m. p. 170° (decomp.) (Found: C, 40·7; H, 3·5; N, 18·9. $C_{25}H_{24}O_{15}N_{10}S$ requires C, 40·7; H, 3·3; N, 19·0%).

Exchange in Deuterium Oxide Solution.—Nuclear magnetic resonance spectra. In the hydrogen nuclear magnetic resonance spectra of a solution of thiamine monohydrate (0·05 g.) in water (0·5 ml.) a sharp peak was observed at 192 cycles/sec. to the lower field side of the resonance of the hydrogen nuclei in the solvent water. This peak was unequivocally assigned to the 2-hydrogen atom in the thiazole ring by comparison with spectra of a series of thiazolium salts, *e.g.*, 3-benzyl-4-methylthiazolium chloride [15] and oxythiamine [16] which give peaks at 203 and 197 cycles/sec. respectively. Thiamine monohydrate (0·25 g.) was dissolved in water (0·25 ml.) and treated with N-sodium hydroxide (0·70 ml., 1 mol.), and the solution was freeze-dried. The dried product was dissolved in deuterium oxide, and the hydrogen nuclear magnetic resonance spectrum examined immediately: the peak at 192 cycles/sec. was no longer detectable.

Similarly, solutions of the homologues (I) and (II) in water showed sharp peaks at 197 and 212 cycles/sec. respectively. After treatment with deuterium oxide, neither of these peaks was detectable.

Measurements were made with a Varian V-4300B high resolution spectrometer at 40 megacycles/sec. For comparison with Breslow's results [10] it should be noted that the resonance of benzene in an external capillary with respect to water occurs at 74 cycles/sec. to the lower field side of the water resonance. Further, because of the different frequency used his frequency separations have to be multiplied by a factor of $\frac{4}{3}$ for comparison with ours, *i.e.*, his quoted resonance frequency for the 2-hydrogen atom 3 : 4-dimethylthiazolium bromide of 108 cycles/sec. would occur at approximately 218 cycles/sec. on our scale.

Infrared spectra. 4-Methyl-3-phenethylthiazolium bromide,[11] when kept in deuterium oxide at room temperature for 3 days, then dried in a vacuum, shows a strong C–D stretching band [10] (in Nujol) at 2275 cm.$^{-1}$. This is supported by the disappearance of a band at 876 cm.$^{-1}$ which can be assigned to the out-of-plane bending of the 2-hydrogen atom.[10] Similarly thiamine shows the new band at 2280 cm.$^{-1}$ and the loss of a band at 897 cm.$^{-1}$.

The solution of the homologue (I) in deuterium oxide used for the nuclear magnetic resonance spectra was freeze-dried, and the infrared spectrum of the product examined. This showed the appearance of a band at 2300 cm.$^{-1}$ consistent with a C–D stretching frequency, and loss of a band at 913 cm.$^{-1}$ consistent with an out-of-plane bending of the 2-hydrogen atom. Comparable spectra for the homologue (II) are not available owing to difficulty in obtaining a satisfactory mull.

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[15] Karimullah, *J.*, 1937, 961.
[16] Rydon, *Biochem. J.*, 1951, **48**, 383.

368. *The Zero Differential Overlap Approximation in Molecular-orbital Calculations.*

By E. Theal Stewart.

The reliability of the zero differential overlap approximation [1-4] has been tested under conditions of widely varying bond length and effective nuclear charge in non-empirical molecular-orbital calculations of electron-repulsion energy in the ground state and the lower excited states of ethylene and hydrogen. The use of the approximation appears to be (*a*) expedient in otherwise intractable computations on $2p\pi$-electron systems (provided these do not go much beyond the limits of sophistication set by Goeppert-Mayer and Sklar [5]); (*b*) inadmissible in $1s\sigma$ systems; [3] and (*c*) hazardous in any systems on which exploratory tests are lacking.

The forbidding aspect of antisymmetrized molecular-orbital calculations on the stationary states of molecules with numerous valency electrons is due chiefly to the tedium of the trivial and reiterative operations involved in the expansion and evaluation of the electron-repulsion integrals. As a means of eliminating the major part of this computational work (at least in $2p\pi$-electron systems), and so removing the barrier to calculations on molecules of any but the most modest size,* Pariser and Parr [1-3] suggested the use of their zero differential overlap approximation.

So promising a simplification in technique warrants rigorous examination. As a first step, we have shown [4] (simply by isolating the electron-repulsion terms in the computed π-electron energies of ethylene and benzene) that in calculations restricted to the observed C–C distances (R_e) and to the conventional [5] value of the so-called "effective nuclear charge" of carbon ($Z = 3{\cdot}18$), the use of Pariser and Parr's approximation is fully justified, if only because the errors which it introduces are dwarfed by the lamentable disparities [6] which still exist between the calculated and the observed energies of unsaturated hydrocarbon molecules.

Several considerations suggest, however, that a non-empirical calculation in which a single value of Z is used for the ground state and each of the excited states is as unlikely to be successful in a molecular system as in an atomic system (cf. Hurley [7]). For this reason, and because of the possible development of some recent work by Phillipson and Mulliken,[8] it seems desirable to ascertain the effects of variations in Z (and, collaterally, in R) on the reliability of the zero differential overlap approximation.

Results for ethylene (treated as a two-electron system [9]) and for hydrogen are now presented. Because of complicating features in many-electron systems, the extension of the preliminary work [4] on benzene will be considered elsewhere. The zero differential overlap approximation breaks down [3] in the calculation of the "vertical" excitation energies of the hydrogen molecule: one of our objects is to investigate whether the approximation is any more successful at the larger values [10] of R_e appropriate to the excited states. (All errors vanish, of course, as R approaches ∞.)

* The twelve-centre, twelve-electron system of diphenyl represents the limit to which complete calculations of electron-repulsion energy have yet been carried (Stewart, *J.*, 1958, 4016).

[1] Pariser and Parr, *J. Chem. Phys.*, 1953, **21**, 466.
[2] *Idem*, *ibid.*, p. 767.
[3] Parr and Pariser, *ibid.*, 1955, **23**, 711.
[4] Stewart, *J.*, 1959, 70.
[5] Goeppert-Mayer and Sklar, *J. Chem. Phys.*, 1938, **6**, 645; Sklar and Lyddane, *ibid.*, 1939, **7**, 374; Parr and Crawford, *ibid.*, 1948, **16**, 1049; Crawford and Parr, *ibid.*, 1949, **17**, 726.
[6] Parr, Craig, and Ross, *ibid.*, 1950, **18**, 1561; Moffitt and Scanlan, *Proc. Roy. Soc.*, 1953, *A*, **218**, 464; 1953, *A*, **220**, 530.
[7] Hurley, *J. Chem. Phys.*, 1958, **28**, 532.
[8] Phillipson and Mulliken, *ibid.*, p. 1248.
[9] Parr and Crawford, *ibid.*, 1948, **16**, 526.
[10] Herzberg, "Spectra of Diatomic Molecules," Van Nostrand, New York, 1950.

Pariser and Parr's Two Approximations.—As well as the zero differential overlap approximation,[1] we have examined a second approximation suggested by Parr and Pariser [3] (the " Mulliken–Parr–Pariser approximation "). In the zero differential overlap approximation all integrals involving overlap between the orbitals of non-identical atoms are disregarded (including, in many-centre systems, all three- and four-centre integrals). The Mulliken–Parr–Pariser approximation is much less drastic, and is an extension to two-centre " ionic " (" hybrid ") and exchange integrals of Mulliken's [11] well-known formula for expanding three- and four-centre integrals in terms of one- and two-centre Coulomb integrals.

Wave Functions and Energies.—For a symmetrical two-centre system of two electrons, the simplest molecular-orbital wave functions [12] forming an orthogonal set can be expanded as follows (in order of increasing energy):

	Symmetry	
	Group $D_{\infty h}$	Group D_{2h}
$^1\Psi_{++} = \frac{1}{2}(1+S)^{-1}(ab+ba+aa+bb)$	$^1A_{1g}$	^1A_g
$^3\Psi_{+-} = 2^{-\frac{1}{2}}(1-S^2)^{-\frac{1}{2}}(ab-ba)$	$^3A_{1u}$	$^3B_{1u}$
$^1\Psi_{+-} = 2^{-\frac{1}{2}}(1-S^2)^{-\frac{1}{2}}(aa-bb)$	$^1A_{1u}$	$^1B_{1u}$
$^1\Psi_{--} = \frac{1}{2}(1-S)^{-1}(ab+ba-aa-bb)$	$^1A_{1g}$	^1A_g

The corresponding electron-repulsion energies are:

$$^1\mathscr{W}_{++} = (1+S)^{-2}(\tfrac{1}{2}C_0 + \tfrac{1}{2}C + 2L + A)$$
$$^3\mathscr{W}_{+-} = (1-S^2)^{-1}(C-A)$$
$$^1\mathscr{W}_{+-} = (1-S^2)^{-1}(C_0-A)$$
$$^1\mathscr{W}_{--} = (1-S)^{-2}(\tfrac{1}{2}C_0 + \tfrac{1}{2}C - 2L + A)$$

S, C, L, and A are Kopineck's [13] symbols (with subscripts removed) for the overlap, Coulomb, ionic, and exchange integrals; C_0 denotes the one-centre Coulomb integral. The effects of the approximations we have examined are:

Mulliken–Parr–Pariser: $L = \frac{1}{2}S(C_0 + C)$, $A = \frac{1}{2}S^2(C_0 + C)$;
Zero differential overlap: $S = 0$, $L = 0$, $A = 0$.

In states represented by the wave functions $^1\Psi_{++}$ or $^1\Psi_{--}$ (but not orthonormal linear combinations of these functions) the two approximations happen to be equivalent.

Results.—In Table 1 are listed the energies of repulsion between the two π electrons of ethylene, calculated both precisely and approximately over wide ranges of Z and R, each parameter being in turn fixed and varied. The corresponding figures for hydrogen are given in Table 2. In each case the choice of constant values of Z may be regarded as arbitrary.

Ethylene. The two approximations work very well in calculations on the ground state of ethylene, leading at worst to errors of 0·15 ev (only 0·05 ev for $Z \sim 3{\cdot}2$ and $R \sim R_e$); they are rather less satisfactory for the excited state ($^1\Psi_{--}$) in which they are equivalent.

In the states where the two approximations diverge ($^3\Psi_{+-}$, $^1\Psi_{+-}$), the zero differential overlap approximation is, as would be expected, the cruder. That it is indeed useless at very short bond lengths is of little practical importance, for molecular-orbital wave functions based on linear combinations of primitive atomic orbitals are bound in any case to break down when $R \ll R_e$; the approximation may be used fairly safely when $ZR/2 > 4{\cdot}0$. [This requirement is not necessarily fulfilled in the calculation of " vertical " excitation energies: the (unknown) optimum values of Z for the excited states may well be significantly less than 3·18.]

Hydrogen. Although the zero differential overlap approximation is very satisfactory

[11] Mulliken, *J. Chim. phys.*, 1949, **46**, 497; Rüdenberg, *J. Chem. Phys.*, 1951, **19**, 1433.
[12] Longuet-Higgins, *Proc. Phys. Soc.*, 1948, **60**, 270.
[13] Kopineck, *Z. Naturforsch.*, 1950, **5a**, 420; 1951, **6a**, 177; 1952, **7a**, 785; Preuss, " Integraltafeln zur Quantenchemie," Springer-Verlag, Berlin, etc., 1956, Vol. I.

in the calculation of the ground-state electron-repulsion energy of hydrogen (astonishingly so in the neighbourhood of R_e), it is manifestly too rough to be used for the excited states,[3] even at the relatively large equilibrium H–H distance observed [10] in the lowest $^1A_{1u}$ state: it is thus valueless in the calculation of excitation energies. The Mulliken–Parr–Pariser approximation is far more trustworthy, except in the $^1\Psi_{--}$ state.

TABLE 1. *Ethylene*: *Electron-repulsion energy* (ev*).

(a) $Z = 3{\cdot}18$; C–C *distance varied.*

$ZR/2$		1·0	2·0	3·0	4·0	5·0	6·0	7·0
C–C distance † (Å *)		0·3328	0·6656	0·9984	1·3313	1·6641	1·9969	2·3297
State	Approximation ‡							
$^1\Psi_{++}$	None	16·507	15·471	14·236	13·115	12·263	11·674	11·269
	M.P.P. or z.d.o.	16·440	15·317	14·126	13·138	12·387	11·822	11·393
$^3\Psi_{+-}$	None	12·958	11·761	10·332	8·933	7·696	6·666	5·841
	M.P.P.	13·646	12·193	10·530	9·001	7·714	6·670	5·841
	z.d.o.	15·947	13·700	11·318	9·342	7·839	6·712	5·853
$^1\Psi_{+-}$	None	18·546	18·010	17·523	17·207	17·041	16·970	16·946
	M.P.P.	19·234	18·442	17·721	17·274	17·059	16·974	16·946
	z.d.o.	16·934	16·934	16·934	16·934	16·934	16·934	16·934
$^1\Psi_{--}$	None	16·356	15·356	14·372	13·454	12·676	12·044	11·542
	M.P.P. or z.d.o.	16·440	15·317	14·126	13·138	12·387	11·822	11·393

(b) Z *varied*; C–C *distance* = 1·353 Å. §

$ZR/2$		2·0	2·5	3·0	3·5	4·0	4·5	5·0
Z †		1·5644	1·9555	2·3467	2·7378	3·1289	3·5200	3·9111
State	Approximation ‡							
$^1\Psi_{++}$	None	7·611	9·135	10·506	11·750	12·904	14·005	15·082
	M.P.P. or z.d.o.	7·535	9·043	10·424	11·709	12·926	14·096	15·234
$^3\Psi_{+-}$	None	5·786	6·798	7·625	8·281	8·790	9·175	9·465
	M.P.P.	5·998	6·984	7·771	8·384	8·856	9·215	9·488
	z.d.o.	6·740	7·672	8·352	8·840	9·191	9·448	9·641
$^1\Psi_{+-}$	None	8·860	10·915	12·931	14·932	16·930	18·936	20·959
	M.P.P.	9·073	11·101	13·077	15·034	16·997	18·977	20·981
	z.d.o.	8·331	10·413	12·496	14·579	16·661	18·744	20·827
$^1\Psi_{--}$	None	7·555	9·141	10·606	11·964	13·238	14·442	15·591
	M.P.P. or z.d.o.	7·535	9·043	10·424	11·709	12·926	14·096	15·234

* A.U. = 27·210 ev; $a_0 = 0{\cdot}52917$ Å (Kauzmann, "Quantum Chemistry," Academic Press Inc., New York, 1957, App. 1).

† Arguments correspond with those of Kopineck,[13] whose numerical values of S, C, L, and A have been used.

‡ M.P.P. = Mulliken–Parr–Pariser; z.d.o. = zero differential overlap.

§ Equilibrium C–C distance in ground state (Gallaway and Barker, *J. Chem. Phys.*, 1942, **10**, 88).

Even in the ground state the zero differential overlap approximation depends for its success upon its accidental equivalence with the Mulliken–Parr–Pariser approximation, and this equivalence seems in turn to depend on the arbitrary balance between "covalent" and "ionic" contributions characteristic of single-configuration molecular-orbital wave functions (Table 3).

The sign of the error resulting from the use of the zero differential overlap approximation with the second wave function of Table 3 is important (cf. $^1\Psi_{++}$, $^1\Psi_{--}$). The approximation disturbs the optimum balance between the component configurations, thus defeating the object of a configuration-interaction calculation.

Conclusions.—The Mulliken–Parr–Pariser is clearly the safer of the two approximations, and the fact that it works equally well with wave functions as dissimilar as those of ethylene and hydrogen suggests that it might be used without undue hazard in calculations on other molecules. But it seems unlikely that any important saving of computational effort would follow from its use in many-centre systems. The present results are of interest, not because they suggest the use of the Mulliken–Parr–Pariser approximation, but because they indirectly support the use of the parent approximation [11] for three- and four-centre integrals.

In many-centre systems the zero differential overlap approximation offers an enormous

TABLE 2. *Hydrogen: Electron-repulsion energy* (ev*).

(a) $Z = 1$; H–H *distance varied.*

ZR		1·0	1·5	2·0	2·5	3·0	3·5	4·0
H–H distance † (Å *)		0·5292	0·7938	1·0583	1·3229	1·5875	1·8521	2·1167
State	Approximation ‡							
$^1\Psi_{++}$	None	16·077	15·224	14·333	13·492	12·754	12·142	11·656
	M.P.P. or z.d.o.	16·047	15·174	14·299	13·515	12·854	12·312	11·871
$^3\Psi_{+-}$	None	12·187	11·105	10·029	9·017	8·093	7·268	6·545
	M.P.P.	12·404	11·310	10·171	9·096	8·128	7·279	6·545
	z.d.o.	15·089	13·341	11·591	10·024	8·702	7·617	6·736
$^1\Psi_{+-}$	None	19·474	18·833	18·284	17·856	17·545	17·334	17·197
	M.P.P.	19·691	19·038	18·426	17·935	17·580	17·344	17·197
	z.d.o.	17·006	17·006	17·006	17·006	17·006	17·006	17·006
$^1\Psi_{--}$	None	16·717	15·767	14·888	14·107	13·426	12·838	12·334
	M.P.P. or z.d.o.	16·047	15·174	14·299	13·515	12·854	12·312	11·871

(b) Z *varied* §; H–H *distance constant.*

		H–H distance = 0·74166 Å §			H–H distance = 1·29270 Å §			
ZR		1·0	1·5	2·0	1·5	2·0	2·5	3·0
Z †		0·7135	1·0702	1·4270	0·6140	0·8187	1·0234	1·2281
State	Approximation ‡							
$^1\Psi_{++}$	None	11·471	16·294	20·452	9·348	11·734	13·808	15·663
	M.P.P. or z.d.o.	11·450	16·240	20·404	9·317	11·706	13·831	15·786
$^3\Psi_{+-}$	None	8·695	11·885	14·312	6·819	8·211	9·227	9·938
	M.P.P.	8·850	12·105	14·514	6·945	8·327	9·308	9·981
	z.d.o.	10·766	14·279	16·540	8·192	9·489	10·258	10·686
$^1\Psi_{+-}$	None	13·894	20·156	26·091	11·564	14·969	18·273	21·547
	M.P.P.	14·049	20·376	26·293	11·690	15·085	18·354	21·590
	z.d.o.	12·134	18·201	24·268	10·442	13·923	17·404	20·885
$^1\Psi_{--}$	None	11·927	16·874	21·244	9·681	12·189	14·437	16·488
	M.P.P. or z.d.o.	11·450	16·240	20·404	9·317	11·706	13·831	15·786

*‡ See footnotes to Table 1.

† Arguments correspond with those of Hirschfelder and Linnett (*J. Chem. Phys.*, 1950, **18**, 130), whose numerical values of S, C, L, and A (present notation) have been used.

§ Equilibrium H–H distances: 0·74166 Å in the ground state; 1·29270 Å in the lowest $^1A_{1u}$ state.[10] The corresponding optimum values of Z are 1·19 and 0·79.

TABLE 3. *Hydrogen: Ground-state electron-repulsion energy* (ev*) *for various wave functions.*

H–H *distance* = 0·74166 Å.§

Z †		0·7135	1·0702	1·4270
Wave function	Approximation ‡			
Molecular-orbital ($^1\Psi_{++}$)	None	11·471	16·294	20·453
	M.P.P. or z.d.o.	11·450	16·240	20·404
Molecular-orbital with configuration interaction	None	10·891	15·389	19·103
	M.P.P.	10·853	15·314	19·023
	z.d.o.	11·407	16·028	19·800
Valency-bond (purely " covalent ")	None	11·079	15·023	17·628
	M.P.P.	11·056	14·955	17·529
	z.d.o.	10·766	14·279	16·540

*‡ See footnotes to Table 1. †§ See footnotes to Table 2.

advantage; and, although some of the disparities in Table 1 are large enough to be disturbing, there seems to be adequate justification for the use of the approximation in calculations on the $2p\pi$ *wave functions of conjugated or aromatic molecules* which would otherwise be unrewardingly long.

It is probably undesirable, however, that the approximation should be used in non-empirical calculations embodying quasi-variational complicacies such as interacting configurations, self-consistent * orbitals, or sets of wave functions with non-uniform values of

* In Roothaan's sense (*Rev. Mod. Physics*, 1951, **23**, 69). The term " self-consistent " (often with the odd addition of the word " field ") is now commonly used to describe essentially empirical calculations in which allowance is made for the energy of repulsion between electron distributions described by unmodified Hückel orbitals. This usage can sometimes be as perplexing to the theoretician as it must always be to the experimentalist interested in the results of quantum-chemical calculations, but not the techniques.

Z. Errors of the same order as those in 1sσ systems (Table 3) are not to be expected; but there is some danger that the zero differential overlap approximation may invalidate calculations purporting to transcend the limitations of the original Goeppert-Mayer–Sklar procedure.[5,9]

This publication was prompted by a Referee's comment on an earlier paper.[4] The work was carried out during the tenure of Carnegie and Junior Deeds Research Fellowships.

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369. *Reactions of Peroxides in* NN-*Dimethylformamide Solution. Part I. The Induced Decomposition of Benzoyl Peroxide.*

By C. H. BAMFORD and E. F. T. WHITE.

The thermal decomposition of benzoyl peroxide in *NN*-dimethylformamide solution has been studied between 40° and 70°. A rapid induced decomposition was observed, of first order in benzoyl peroxide. Interaction of benzoyloxy-radicals and the solvent forms H·CO·NMe·CH_2· radicals which readily attack the peroxide molecules; a chain mechanism in which termination occurs by combination of H·CO·NMe·CH_2· and benzoyloxy-radicals is thus established. Benzoic acid and *N*-benzoyloxymethyl-*N*-methylformamide are major products; the structure of the latter has been established by synthesis. The significance of these results in polymerization studies in *NN*-dimethylformamide is discussed.

NN-DIMETHYLFORMAMIDE has recently been extensively used as a polymerization solvent and several kinetic studies in this medium, particularly of the polymerization of acrylonitrile, have been reported.[1,2] As we learn more about the mechanism of polymerization we need to know how and how much the amide may participate in the reactions. It may react with polymer radicals or with primary radicals arising directly from the initiator. Chain transfer occurs with several types of polymer radical [3] but the point of radical attack has not hitherto been established. We now report a study of reactions between *NN*-dimethylformamide and primary radicals derived from benzoyl peroxide.

RESULTS AND DISCUSSION

General Features of the Reaction.—Benzoyl peroxide decomposes in *NN*-dimethylformamide solution by a first-order process. Plots of the logarithms of the peroxide concentration against time were linear over at least 90% of the reaction, and had similar slopes over the whole range of initial concentrations studied (4—60 $\times$ 10^{-2} mole $l.^{-1}$).

Temp.	40°	60°	69·4°	70°
Half-life (min.)	3000	154	61·5	59
Overall velocity coefficient k ($sec.^{-1}$)	$3{\cdot}86 \times 10^{-4}$	$7{\cdot}50 \times 10^{-3}$	$1{\cdot}88 \times 10^{-4}$	$1{\cdot}96 \times 10^{-4}$

The Table summarizes the rate data obtained at several temperatures. The values of k correspond closely to the Arrhenius relation $k = 3 \times 10^{14} \exp(-28{,}300/RT)$ $sec.^{-1}$. By contrast, the half-life of the decomposition at 69·4° measured in the presence of styrene ($\sim$ 1 mole $l.^{-1}$) is about 30 hr. so, in the absence of a benzoyloxy-radical scavenger such as styrene, a rapid induced decomposition of the peroxide occurs.

[1] Onyon, *Trans. Faraday Soc.*, 1956, **52**, 80; Barson, Bevington, and Eaves, *Trans. Faraday Soc.*, 1958, **54**, 1678; Thomas, Gleason, and Pellon, *J. Polymer Sci.*, 1955, **17**, 275.
[2] Bamford and Jenkins, *Proc. Roy. Soc.*, 1953, *A*, **216**, 515; Bamford, Jenkins, and Johnston, *ibid.*, 1957, *A*, **239**, 214.
[3] Prévot-Bernas and Sebban-Danon, *J. Chim. phys.*, 1956, **53**, 418; Bamford, Jenkins, Johnston, and White, *Trans. Faraday Soc.*, 1959, **55**, 168; also unpublished work.

The main products of the induced reaction are the ester *N*-benzoyloxymethyl-*N*-methylformamide (I) and benzoic acid. The former was isolated (not quantitatively) in approximately 60 mole % yield, and its constitution has been confirmed by hydrolysis to benzoic acid, methylamine, and formaldehyde, and also by synthesis. The yield of benzoic acid is ~85 mole % throughout the course of the reaction at 60°. Comparatively small amounts of carbon dioxide are formed during the decomposition: at 50° and 60° 10·7 and 11·5 mole % respectively, based on the benzoyl peroxide decomposed.

The primary step in the thermal decomposition of benzoyl peroxide in many solvents is the homolytic fission into benzoyloxy-radicals:

$$(Ph\cdot CO\cdot O)_2 \longrightarrow 2Ph\cdot CO\cdot O\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

It is well known [4,5] that these radicals may attack further peroxide molecules, causing an induced decomposition of the latter into carbon dioxide, phenyl benzoate, and biphenyl; in *NN*-dimethylformamide no biphenyl or phenyl benzoate could be detected. Since the yield of carbon dioxide is low, most of the benzoyloxy-radicals formed in (1) must attack the solvent, giving rise to reactions (2), (3), and (4):

$$Ph\cdot CO\cdot O\cdot + H\cdot CO\cdot NMe_2 \longrightarrow Ph\cdot CO_2H + H\cdot CO\cdot NMe\cdot CH_2\cdot \quad . \quad . \quad . \quad . \quad (2)$$

$$H\cdot CO\cdot NMe\cdot CH_2\cdot + (Ph\cdot CO\cdot O)_2 \longrightarrow H\cdot CO\cdot NMe\cdot CH_2\cdot O\cdot COPh\ (I) + Ph\cdot CO\cdot O\cdot \quad . \quad (3)$$

$$H\cdot CO\cdot NMe\cdot CH_2\cdot + Ph\cdot CO\cdot O\cdot \longrightarrow H\cdot CO\cdot NMe\cdot CH_2\cdot O\cdot COPh \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Reactions (3) and (4) constitute a chain mechanism responsible for the rapid induced decomposition of the peroxide into the observed products.

Kinetics.—The velocity coefficients of reactions (1)—(4) will be denoted by k_1, k_2, k_3, k_4, and for conciseness P, P·, D, D· will be used to represent benzoyl peroxide, the benzoyloxy-radical, *NN*-dimethylformamide, and the derived radical H·CO·NMe·CH_2· respectively. On the basis of the usual stationary-state assumptions we have:

$$d[P\cdot]/dt = 2k_1[P] - k_2[P\cdot][D] + k_3[D\cdot][P] - k_4[P\cdot][D\cdot] = 0 \quad . \quad . \quad (5)$$

$$d[D\cdot]/dt = k_2[P\cdot][D] - k_3[D\cdot][P] - k_4[P\cdot][D\cdot] = 0 \quad . \quad . \quad . \quad . \quad (6)$$

These equations may be solved directly for [P·], [D·], and the results used to deduce the following relations:

$$-\frac{d[P]}{dt} = \frac{d[A]}{dt} = \frac{k_1[P]}{2}\{1 + (1 + 4y[D])^{\frac{1}{2}}\} \quad . \quad . \quad . \quad . \quad . \quad (7)$$

where [A] represents the concentration of benzoic acid and $y = k_2k_3/k_1k_4$. It is clear from (7) that according to this mechanism the reaction should be of first order in peroxide with an overall velocity constant given by (8):

$$k = \tfrac{1}{2}k_1\{1 + (1 + 4y[D])^{\frac{1}{2}}\} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

and that the benzoic acid formed should be equivalent to the peroxide decomposed, on a molar basis. These predictions are in satisfactory agreement with observation: spontaneous decarboxylation of a minor proportion of the benzoyloxy-radicals could account for the lower yield of benzoic acid observed and also for the small amount of carbon dioxide formed.

If the reaction is carried out in the presence of a radical scavenger (*e.g.*, styrene) the induced decomposition [reactions (2), (3)] is largely suppressed; very similar behaviour was observed by Nozaki and Bartlett [5] and by Swain, Stockmayer, and Clarke [4] for the decomposition of benzoyl peroxide in a number of other solvents. It thus becomes possible to evaluate k_1 directly; the values obtained at 70° were in the range 6·4—8·0 × 10^{-6} sec.$^{-1}$. Unfortunately, the reaction under these conditions is not quite straightforward since the " first-order constant " varies somewhat with the initial peroxide concentration;

[4] Swain, Stockmayer, and Clarke, *J. Amer. Chem. Soc.*, 1950, **72**, 5426.
[5] Nozaki and Bartlett, *ibid.*, 1946, **68**, 1686.

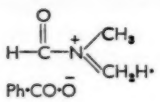
this behaviour, which is not understood, has been observed in other systems containing benzoyl peroxide.[6] For present purposes it will be sufficiently accurate to take $k_1 = 7 \times 10^{-6}$ sec.$^{-1}$. Since k, k_1, and [D] are known, y may be calculated from (8). The value obtained at 70° is 55·1 mole^{-1} l., from which it follows that $k_2k_3/k_4 = 3{\cdot}8 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$. Further evaluation of the individual velocity coefficients is not possible from the present results. The kinetic chain length ν of the induced decomposition, *i.e.*, the number of peroxide molecules decomposed for each P· radical generated in the spontaneous fission (1), is given by

$$\nu = \{(1 + 4y[D])^{\frac{1}{2}} - 1\}/4 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

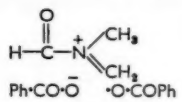
This quantity is therefore independent of the benzoyl peroxide concentration. Its value at 70° in bulk *NN*-dimethylformamide solution is approximately 13.

Chemical Aspects and Significance in Polymerization Studies.—The decomposition of benzoyl peroxide in *NN*-dimethylformamide solution is unusual in that the induced reaction is of first order in peroxide concentration. Generally, the order of an induced decomposition is higher than unity. However, Cass [6,7] observed similar kinetics for the decomposition in diethyl ether, and isolated 1-ethoxyethyl benzoate in good yield, together with benzoic acid. These products clearly arise from a reaction sequence similar to (2), (3), and (4).[4,6,7]

The characteristic kinetic features of the reaction in *NN*-dimethylformamide arise from the dominance of reactions (2), (3), and (4) over other alternatives. The greater strength of the O–H bond than of the C–H bond is consistent with (2) being fast and predominating over decarboxylation of the benzoyloxy-radical. It is noteworthy that, since the O–H bond is also much stronger than the O–C bond, the relative rates of hydrogen abstractions compared to additions to double bonds in polymerization reactions may be much higher for –O· radicals than for $-\overset{|}{\underset{|}{C}}\cdot$ radicals. Reactions (2) and (3) may be facilitated by the stabilization of their transition states by polar contributions from structures such as (II) and (III). Further, it is not surprising that (4), involving interaction of electron-donating and -accepting radicals, should predominate over other possible termination reactions.



(II)



(III)

The mechanism may be compared with that of the reactions between amines and benzoyl peroxide which have been studied by Gambarjan [8] and extensively investigated in recent years by Horner and his co-workers.[9] According to Horner, the primary step is the transfer of an electron from the amine to the peroxide. This is a bimolecular process which is not a chain reaction and it is distinct from an induced decomposition of the type found in the present work. (Urry and Juveland [10] have, however, suggested that an induced decomposition may in fact participate in benzoyl peroxide–amine systems in some circumstances.) However, the mechanism of reactions (2) and (3) resembles the primary step in the amine–peroxide reaction postulated by Horner, insofar as these reactions are assisted by the electrophilic characters of the benzoyloxy-radical and the peroxide and the electron-donating properties of *NN*-dimethylformamide and the derived radical H·CO·NMe·CH_2·. The polar nature of the transition state would, of course, be much more pronounced in the amine–peroxide reaction than in reactions (2) and (3).

[6] Cass, *J. Amer. Chem. Soc.*, 1946, **68**, 1976.
[7] *Idem, ibid.*, 1947, **69**, 500.
[8] Gambarjan, *Ber.*, 1909, **42**, 4003; 1925, **58**, 1775; Gambarjan and Cialtician, *Ber.*, 1927, **60**, 390.
[9] A concise discussion of Horner's work, with references, is given in Walling, "Free Radicals in Solution," John Wiley and Sons, 1957, p. 590.
[10] Urry and Juveland, *J. Amer. Chem. Soc.*, 1958, **80**, 3322.

The possible occurrence of (2) must be considered when studying vinyl polymerization in *NN*-dimethylformamide; this is particularly necessary when kinetic chain lengths are to be determined by estimation of the number of initiator fragments incorporated into polymer molecules. At low monomer concentrations, reaction (2) may compete significantly with direct initiation by addition of benzoyloxy-radicals to the monomer; initiation may then occur through $H{\cdot}CO{\cdot}NMe{\cdot}CH_2{\cdot}$ radicals, but the polymer will not carry end-groups derived from the initiator. Estimates of the kinetic chain length from end-group determinations will therefore be too high, while initiator efficiencies will appear to be too low. Barson, Bevington, and Eaves,[1] studying the polymerization of acrylonitrile in *NN*-dimethylformamide with labelled benzoyl peroxide as initiator, have, in fact, recorded behaviour of this type. Although the authors account for their results by postulating hydrogen-transfer between benzoyloxy-radicals and the monomer, we consider it much more likely that the radicals react according to (2), since the amide solvent has a higher transfer constant (in the polymerization of acrylonitrile) than the monomer [3,11] and was present in greater concentration.

Experimental

Materials.—Benzoyl peroxide was purified by two precipitations from chloroform solution into methanol and was dried in a vacuum. *NN*-Dimethylformamide was treated with phosphoric oxide several times before vacuum distillation.[2]

Technique.—The decomposition was carried out in the dark under nitrogen, and its progress was followed by titrating samples by the method of Swain, Stockmayer, and Clarke.[4] In some cases the benzoic acid was estimated at intervals during a reaction. For this purpose samples were taken from the reaction mixture, diluted with *NN*-dimethylformamide, and titrated with standard potassium methoxide in benzene–methanol solution to a thymol-blue end-point.

Estimations of the carbon dioxide evolved during the reaction were made by sweeping out the carbon dioxide by a stream of nitrogen, which was then bubbled through standard baryta.

Isolation of N-*Benzoyloxymethyl*-N-*methylformamide* (I).—After decomposition of benzoyl peroxide in *NN*-dimethylformamide most of the solvent was removed by vacuum-distillation, and the residue, in ether solution, was washed with dilute aqueous sodium carbonate to remove benzoic acid. The ethereal extract was then dried ($CaSO_4$), and the ether removed. The liquid residue was distilled in a molecular still and gave a colourless oily product with n_D^{20} 1·5398 (Found: C, 62·5; H, 5·7; N, 7·1. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·3%). An indication of the structure of the *product* was first obtained by hydrolysis. When it was treated with 20% aqueous sulphuric acid, formaldehyde was evolved and identified by its characteristic odour and by formation of its 2 : 4-dinitrophenylhydrazone (m. p. and mixed m. p. 164°). On alkaline hydrolysis (50% aqueous sodium hydroxide) methylamine was formed. It gave a characteristic yellow precipitate with Nessler's reagent and a positive carbylamine test. Benzoic acid was produced in both hydrolyses and was identified by a mixed m. p. determination.

Synthesis of N-*Benzoyloxymethyl*-N-*methylformamide.*—Redistilled *N*-methylformamide (59 g.) was refluxed for 1 hr. in alcohol (100 ml.) with paraformaldehyde (31 g.) and potassium carbonate (1 g.). The alcohol was distilled off, and the liquid residue extracted with ether. The insoluble portion consisted mainly of *N*-hydroxymethyl-*N*-methylformamide together with potassium carbonate, which was filtered off. The unpurified material (yield 72%) was used directly for the preparation of the *benzoate* as follows: 9 g. of it were shaken with redistilled benzoyl chloride (11·5 ml.) and 5% aqueous sodium hydroxide (120 ml.) in the cold. The lower layer was separated, washed with dilute sodium carbonate solution, and dried (yield 52%). The product, when distilled in a molecular still, gave a viscous colourless oil with n_D^{20} 1·5401 (Found: C, 63·0; H, 6·0; N, 7·3. $C_{10}H_{11}O_3N$ requires C, 62·2; H, 5·7; N, 7·3%). On hydrolysis this compound behaved identically with the reaction product described above.

The authors thank Miss P. A. Smith for experimental assistance and Mr. M. Lonsdale for the microanalyses.

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Research Laboratory, Maidenhead, Berks. [*Received, January 2nd,* 1959.]

[11] Bamford, Jenkins, and White, *J. Polymer Sci.*, 1959, **34**, 271.

370. *Studies of Trifluoroacetic Acid. Part XVII.* Reaction of Acyl Trifluoroacetates with* βC-, β-, *and* α-*Acetals of* D-*Glucitol.*†

By E. J. Bourne, J. Burdon, and J. C. Tatlow.

β- and α-Methylene [1] derivatives of D-glucitol react with equimolecular mixtures of acetic, benzoic, or propionic acid and trifluoroacetic anhydride to give, after mild hydrolysis, D-glucitol derivatives *O*-acylated in the primary positions and with free hydroxyl groups in the secondary positions. With benzylidene and *iso*propylidene derivatives of D-mannitol and D-glucitol, the fully acetylated hexitols are produced.

In Part XIV [2] it was shown that treatment of 1 : 6-di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-methylene-D-glucitol with an equimolecular mixture of a carboxylic acid and trifluoroacetic anhydride caused rupture of the βT-ring [1] (3 : 5), but not of the βC-ring (2 : 4). Related investigations are now reported for methylene derivatives of D-glucitol containing β- and α-rings. These rings also are broken, and in a similar manner to that described by Ness, Hann, and Hudson,[3] who used a mixture of acetic acid, acetic anhydride, and concentrated sulphuric acid and obtained products with an *O*-acetyl group in the primary position and an *O*-acetoxymethyl group in the secondary position for each ring that was broken. It is now shown that, with an equimolecular mixture of acetic, propionic, or benzoic acid, and trifluoroacetic anhydride, β- and α-methylene rings break to give, after mild hydrolysis which presumably removes trifluoroacetoxymethyl residues, D-glucitol derivatives *O*-acylated in the primary positions and with hydroxyl groups in the secondary positions. The work described here and in Part XIV [2] illustrates a new approach to the synthesis of partly substituted polyhydroxy-compounds.

Treatment of 5 : 6-di-*O*-acetyl-1 : 3-2 : 4-di-*O*-methylene-D-glucitol (I) with an equimolecular mixture of acetic acid and trifluoroacetic anhydride (3 mol. each) for 7 hr. at 25° yielded, after mild hydrolysis, a crystalline tri-*O*-acetyl-*O*-methylenehexitol, which was acetylated to give the known 1 : 3 : 5 : 6-tetra-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (II). The same triacetate was obtained by a similar acetolysis and subsequent hydrolysis of 1 : 6-di-*O*-acetyl-2 : 4-3 : 5-di-*O*-methylene-D-glucitol (III), which showed that it was 1 : 5 : 6-tri-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (IV), as would be expected from the results described in Part XIV.[2] Thus the 1 : 3-*O*-methylene ring (β) had broken in the expected manner to give a 1-*O*-acetyl group and a free 3-hydroxyl group, leaving the 2 : 4-ring (βC) intact.

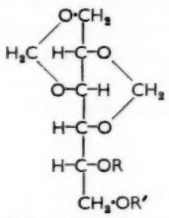
1 : 3-2 : 4-Di-*O*-methylene-D-glucitol (V) was preferentially benzoylated to give a compound (VI) believed to be the 6-benzoate. This afforded the 5-acetate 6-benzoate (VII) on acetylation. Treatment of this diester with benzoic acid and trifluoroacetic anhydride (3 mol. each) for 12 hr. at 25° gave a product which was readily hydrolysed to 5-*O*-acetyl-1 : 6-di-*O*-benzoyl-2 : 4-*O*-methylene-D-glucitol (VIII), identical with the material prepared previously [2] from 1 : 6-di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-methylene-D-glucitol. The two independent syntheses of compound (VIII) together show (*a*) that the benzoate groups in (VI) and (VII) were in fact located on position 6; (*b*) that the 1 : 3-*O*-methylene ring of (VII) had been ruptured in the same way as that of (I); and (*c*) that the structure allocated to (VIII) in the earlier work [2] was correct. Tri-*O*-methylene-D-glucitol (IX), prepared by an improved method, which resembled that of Ness, Hann, and Hudson [4] for

* Part XVI, *J.*, 1958, 3945.
† Presented in part at XIVth Internat. Congr. Pure Appl. Chem., Zurich, 1955.

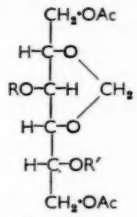
[1] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 137.
[2] Bourne, Burdon, and Tatlow, *J.*, 1958, 1274.
[3] Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 665.
[4] *Idem, ibid.*, 1943, **65**, 2215.

the preparation of tri-*O*-methylene-D-mannitol, reacted similarly with benzoic acid–trifluoroacetic anhydride (4·5 mol. each) to give finally the known [2] 1 : 6-di-*O*-benzoyl-2 : 4-*O*-methylene-D-glucitol (X).

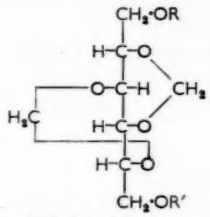
It follows that tri-*O*-methylene-D-glucitol (IX) should react with acetic acid–trifluoroacetic anhydride to give, after mild hydrolysis, 1 : 6-di-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (XI) and this was very probably the case, since a syrup was obtained which gave the expected analytical values. This syrup was acetylated to give the known 1 : 3 : 5 : 6-tetra-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (II), and methylation demonstrated the presence of two free hydroxyl groups. However, a direct proof of the structure of this compound (XI) has not been obtained, as attempts to prepare crystalline derivatives failed: for example, attempted esterifications with benzoyl chloride in pyridine and with benzoic acid–trifluoroacetic anhydride, propionylation, tosylation, and nitration gave syrups. Attempted condensation with formaldehyde gave either tri-*O*-methylene-D-



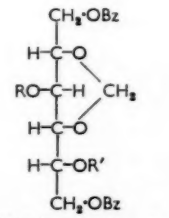
(I) R = R′ = Ac
(V) R = R′ = H
(VI) R = H, R′ = Bz
(VII) R = Ac, R′ = Bz



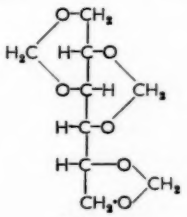
(II) R = R′ = Ac
(IV) R = H, R′ = Ac
(XI) R = R′ = H
(XII) R = R′ = CF_3·CO·O·CH_2
(XIII) R = R′ = CH_3·CO·O·CH_2



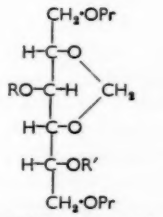
(III) R = R′ = Ac
(XVI) R = R′ = Pr



(VIII) R = H, R′ = Ac
(X) R = R′ = H



(IX)



(XIV) R = R′ = H
(XV) R = R′ = Ac

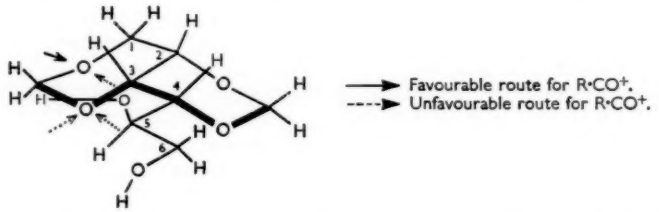
glucitol (IX) or the original syrup (XI). The supposition that the acetate groups were at positions 1 and 6 is supported by the analogous reaction of the triacetal (IX) with propionic acid–trifluoroacetic anhydride (see below) and by the fact that the 1 : 3(β)-ring in the diacetal has already been shown to yield a 1-acetate. Several attempts were made, under rigorously anhydrous conditions, to isolate the intermediate in the formation of the 1 : 6-diacetate (XI); in every case a fluorine-containing syrup was obtained which smelled strongly of trifluoroacetic acid and formaldehyde. It was probably impure 1 : 6-di-*O*-acetyl-2 : 4-*O*-methylene-3 : 5-bis-*O*-trifluoroacetoxymethyl-D-glucitol (XII), contaminated with the diacetate (XI) produced by hydrolysis with atmospheric moisture. With a ten-fold excess of acetic acid over trifluoroacetic anhydride, tri-*O*-methylene-D-glucitol gave 3 : 5-di-*O*-acetoxymethyl-1 : 6-di-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (XIII), identical with the compound obtained by the method of Ness *et al.*[3] (see Part XIV [2] for a discussion of this reaction).

An equimolecular mixture of propionic acid and trifluoroacetic anhydride converted tri-*O*-methylene-D-glucitol (IX) into 2 : 4-*O*-methylene-1 : 6-di-*O*-propionyl-D-glucitol (XIV), as was shown by its hydrolysis to 2 : 4-*O*-methylene-D-glucitol and by the formation

of its 3 : 5-diacetate (XV). The structure of this diacetate was proved by its synthesis by an alternative route, which involved treatment of 2 : 4-3 : 5-di-*O*-methylene-1 : 6-di-*O*-propionyl-D-glucitol (XVI) with acetic acid–trifluoroacetic anhydride, mild hydrolysis of the product, and acetylation (cf. Part XIV [2]).

Thus it has been established that 1 : 3(β)- and 5 : 6(α)-rings in methylene acetals of glucitol can be ruptured under very mild conditions with equimolecular mixtures of trifluoroacetic anhydride and carboxylic acids, leaving ester groups at the primary positions. Under the same conditions, there is no detectable attack on 2 : 4(βC)-methylene rings; it will be recalled that βC-acetals are also the most resistant to hydrolysis with aqueous acid.[1]

It was suggested in Part XIV [2] that the unsymmetric anhydride ($R{\cdot}CO{\cdot}O{\cdot}CO{\cdot}CF_3$), in its ionic form $[(R{\cdot}CO)^+(O{\cdot}CO{\cdot}CF_3)^-]$, is the component of an equimolecular mixture of a carboxylic acid and trifluoroacetic anhydride which is responsible for the fission of methylene acetals. Some direct supporting evidence has now been obtained since with acetyl trifluoroacetate alone there was no indication that either methylene or the more reactive (see below) benzylidene groups were affected. In esterifications with acetyl trifluoroacetate [5] the presence of trifluoroacetic acid has a pronounced effect and seems to favour ionic processes. In a 1 : 3-2 : 4-diacetal of D-glucitol, the acylium ion ($R{\cdot}CO^+$) could form an oxonium complex with each of the oxygen atoms involved in the β-ring, and



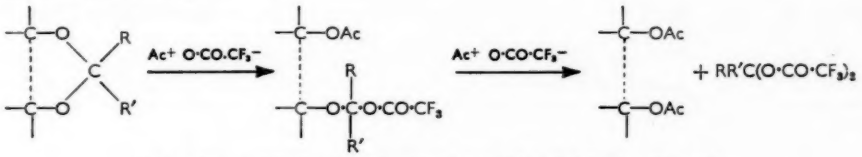
the ion could approach from an axial or an equatorial direction. The most probable conformation of the diacetal is shown in the Figure and it will be seen that an axial approach is improbable at each of the oxygen positions, because of non-bonded interactions analogous to the 1 : 3-diaxial interactions of *cyclo*hexane. Further, the same type of interaction would impede an equatorial approach to the oxygen atom at position 3 so that an equatorial approach to the oxygen atom at position 1 is by far the more probable, to give the 1-ester of the 2 : 4-acetal. With 1 : 3-2 : 4-5 : 6-tri-*O*-methylene-D-glucitol, the 5 : 6(α)-ring is known to be easily the most labile towards acidic reagents,[1,6] so that this will be ruptured first, by attack of the acylium ion at the more accessible oxygen atom at position 6, to give initially the 6-ester of the 1 : 3-2 : 4-diacetal.

Hann, Hudson, and their co-workers [7,8] also showed that a mixture of acetic acid, acetic anhydride, and concentrated sulphuric acid would completely remove a benzylidene acetal ring of any type to give the corresponding diacetate. We have now shown that an equimolecular mixture of acetic acid and trifluoroacetic anhydride reacts in the same way with both benzylidene acetals and *iso*propylidene ketals. For example, 3 : 4-di-*O*-acetyl-1 : 2-5 : 6-di-*O*-*iso*propylidene-D-mannitol, on being treated for 2 hr. at 25°, gave a small yield (21%) of mannitol hexa-acetate. 1 : 3-2 : 5-4 : 6-Tri-*O*-benzylidene-D-mannitol, treated similarly for 24 hr., gave a 39% yield of the same compound together with a 73% yield of benzaldehyde, isolated as its 2 : 4-dinitrophenylhydrazone. The expected benzylidene bistrifluoroacetate could not be isolated. 1 : 3 : 5 : 6-Tetra-*O*-acetyl-2 : 4-*O*-benzylidene-D-glucitol gave D-glucitol hexa-acetate (85%) and benzaldehyde 2 : 4-dinitrophenylhydrazone (74%) under the same conditions, so that even the 2 : 4(βC)-ring was

[5] Bourne, Stacey, Tatlow, and Worrall, *J.*, 1958, 3268.
[6] Barker, Bourne, and Whiffen, *J.*, 1952, 3865.
[7] Haskins, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1942, **64**, 132, 136, 137, 1614.
[8] Wolfe, Hann, and Hudson, *ibid.*, p. 1493.

ruptured here. {Vargha [9] gave m. p. 87—88° and $[\alpha]_D$ −6·7° (in $CHCl_3$) for 1 : 3 : 5 : 6-tetra-*O*-acetyl-2 : 4-*O*-benzylidene-D-glucitol, whereas we find m. p. 121° and $[\alpha]_D$ −5·2° (in $CHCl_3$). Our compound gave correct analyses and was deacetylated to the original 2 : 4-*O*-benzylidene-D-glucitol.} In these three experiments there was considerable darkening of the reaction mixtures and it is interesting that acetone, benzaldehyde, D-glucitol, or D-mannitol alone do not darken under these conditions.

The mechanism of the acetolysis of these benzylidene and *iso*propylidene compounds probably follows the same path as that suggested [2] for the methylene acetals as far as the trifluoroacetoxymethyl ether, which is then subjected to further attack by the unsymmetric anhydride, as follows:



(Benzylidene acetals, R = Ph, R′ = H; *iso*propylidene ketals, R = R′ = Me)

The much greater reactivity of the benzylidene and *iso*propylidene compounds than of methylene acetals reflects their known stabilities to acid and may be due to two factors: (i) oxonium-ion formation will be aided by the inductive effect of the methyl groups with *iso*propylidene ketals and by resonance effects for the benzylidene acetals; (ii) the positive ion formed initially on ring scission [2] will be more stable with both *iso*propylidene and benzylidene compounds and will therefore be more likely to combine with a trifluoroacetate ion. From arguments advanced by Ingold [10] for the hydrolysis of acyclic acetals, the latter seems the most likely explanation, although difference in reactivity of different ring types of the same acetal must be due mainly to ring strain and accessibility of the oxygen atoms.

The usefulness of trifluoroacetic anhydride as an esterification catalyst [11] is not seriously limited as a consequence of the reactions described in this paper and in Part XIV; [2] hydroxyl groups in acetals can still be acetylated in reasonable yield (see p. 1870) with a slight excess of an equimolecular mixture of acetic acid and trifluoroacetic anhydride, without much accompanying ring scission. Even under these conditions, however, *iso*propylidene ketals give negligible amounts of ketal acetates. This must mean that with acetals esterification is much faster than ring scission, whereas with *iso*propylidene ketals the rates are comparable. In connection with this, it has been shown [5] that simple alcohols are almost fully esterified in a few minutes. An earlier report [12] that a derivative of 4 : 6-*O*-benzylideneglucose can be esterified in 64% yield with acetic acid–trifluoroacetic anhydride is consistent with these observations.

Experimental

Methylenation of D-*Glucitol.*—A mixture of D-glucitol (50 g.), 40% formaldehyde solution (70 ml.), and concentrated hydrochloric acid (70 ml.) was kept at 100°. The acetal was gradually precipitated and after 1 hr. the solution was cooled and filtered. The solid gave 1 : 3-2 : 4-5 : 6-tri-*O*-methylene-D-glucitol (23 g.), m. p. and mixed m. p. 208—210° (from ethanol), $[\alpha]_D^{16}$ −27·5° (*c* 2·31 in $CHCl_3$). Ness *et al.*[3] gave m. p. 212—216° and $[\alpha]_D^{20}$ −30·8° (in $CHCl_3$).

The original filtrate was neutralised with sodium carbonate and evaporated to dryness *in vacuo*. The residue was extracted exhaustively with boiling chloroform; the extracts

[9] Vargha, *Magyar Kém. Folyóirat*, 1934, **40**, 151.
[10] Ingold, " Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 334.
[11] Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2976.
[12] Bourne, Stacey, Tatlow, and Tatlow, *J.*, 1951, 826.

deposited a crystalline solid which was recrystallised from ethanol, to give 1 : 3-2 : 4-di-*O*-methylene-D-glucitol (6·2 g.), m. p. and mixed m. p. 173—174°, $[\alpha]_D^{17}$ −27·2° (*c* 2·34 in H_2O). Ness *et al.*[3] gave m. p. 174—175° and $[\alpha]_D^{20}$ −29·6° (in H_2O).

1 : 5 : 6-*Tri*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*.—(*a*) 5 : 6-Di-*O*-acetyl-1 : 3-2 : 4-di-*O*-methylene-D-glucitol, prepared from 1 : 3-2 : 4-di-*O*-methylene-D-glucitol and acetic anhydride in pyridine, had m. p. 135—136° and $[\alpha]_D^{17}$ −11·9° (*c* 2·79 in $CHCl_3$). Ness *et al.*[3] gave m. p. 135—136° and $[\alpha]_D^{20}$ −12·8° (in $CHCl_3$). A solution of this diacetate (1·00 g.) in trifluoroacetic anhydride (3 mol.) and acetic acid (3 mol.) was kept at 25° for 7 hr. (constant rotation), then poured into sodium hydrogen carbonate solution, and the precipitate was extracted with chloroform. Evaporation of the dried ($MgSO_4$) extracts left a syrup which crystallised from ethanol to give 1 : 5 : 6-*tri*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol* (0·80 g.), m. p. 125—126°, $[\alpha]_D^{21}$ +2·4° (*c* 2·47 in $CHCl_3$) (Found: C, 48·1; H, 6·0; Ac, 40·7. $C_{13}H_{20}O_9$ requires C, 48·75; H, 6·3; Ac, 40·3%).

(*b*) 1 : 6-Di-*O*-acetyl-2 : 4-3 : 5-di-*O*-methylene-D-glucitol, prepared by the method of Hann *et al.*,[13] had m. p. 113—114° and $[\alpha]_D^{21}$ +5·7° (*c* 1·72 in $CHCl_3$). These authors gave m. p. 114° and $[\alpha]_D$ +6·6° (in $CHCl_3$). A solution of this compound (0·40 g.) in trifluoroacetic anhydride (3 mol.) and acetic acid (3 mol.) was kept at 25° for 3 hr. and then treated as in (*a*) to give 1 : 5 : 6-tri-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (0·31 g.), m. p. 125—126° alone and on admixture with the above specimen, $[\alpha]_D^{19}$ +2·2° (*c* 1·04 in $CHCl_3$) (Found: C, 48·2; H, 6·3%).

1 : 3 : 5 : 6-*Tetra*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol from* 1 : 5 : 6-*Tri*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*.—The product from (*a*) (0·47 g.), with acetic anhydride in pyridine, gave the tetra-acetate (0·43 g.), m. p. and mixed m. p. 150—151° (aqueous ethanol), $[\alpha]_D^{17}$ −2·1° (*c* 1·34 in $CHCl_3$) (Found: C, 49·3; H, 5·8. Calc. for $C_{15}H_{22}O_{10}$: C, 49·7; H, 6·1%). Ness *et al.*[3] gave m. p. 150—151° and $[\alpha]_D^{20}$ −1·5° (in $CHCl_3$).

1 : 5 : 6-*Tri*-O-*acetyl*-2 : 4-O-*methylene*-3-O-*propionyl*-D-*glucitol*.—The product from (*a*) (0·60 g.), trifluoroacetic anhydride (0·66 ml.), and propionic acid (0·23 ml.) were kept at room temperature for 15 hr., and poured into sodium hydrogen carbonate solution. The precipitate gave the 3-*propionate* (0·38 g.), m. p. 139—140° (from aqueous ethanol), $[\alpha]_D^{20}$ +1·0° (*c* 1·00 in $CHCl_3$) (Found: C, 51·0; H, 6·3%; N-alkali uptake, 10·73 ml./g. $C_{16}H_{24}O_{10}$ requires C, 51·1; H, 6·4%; N-alkali uptake, 10·64 ml./g.). The product from (*b*) gave the same propionate.

6-O-*Benzoyl*-1 : 3-2 : 4-*di*-O-*methylene*-D-*glucitol*.—To an ice-cold solution of 1 : 3-2 : 4-di-*O*-methylene-D-glucitol (3·00 g.) in pyridine (200 ml.), benzoyl chloride (1 mol.) was added dropwise, with shaking. After 3 hr. at room temperature, the 6-benzoate (1·41 g.) was isolated in the usual way; it had m. p. 196—197° (from aqueous ethanol) alone and on admixture with the compound obtained by Bourne and Wiggins,[14] and $[\alpha]_D^{19}$ −14·7° (*c* 2·31 in $CHCl_3$) (Found: C, 58·7; H, 5·8. Calc. for $C_{15}H_{18}O_7$: C, 58·1; H, 5·8%). Bourne and Wiggins [14] reported a monobenzoate (prepared by Schotten–Baumann benzoylation) with m. p. 195—197° and $[\alpha]_D$ −15·9° (in $CHCl_3$).

5-O-*Acetyl*-6-O-*benzoyl*-1 : 3-2 : 4-*di*-O-*methylene*-D-*glucitol*.—6-*O*-Benzoyl-1 : 3-2 : 4-di-*O*-methylene-D-glucitol (0·60 g.) with acetic anhydride in pyridine gave the 5-*acetate* (0·52 g.), m. p. 101° (from aqueous ethanol), $[\alpha]_D^{18}$ −36·1° (*c* 1·55 in $CHCl_3$) (Found: C, 58·3; H, 5·5%; N-alkali uptake, 5·78 ml./g. $C_{17}H_{20}O_8$ requires C, 57·95; H, 5·7%; N-alkali uptake, 5·68 ml./g.).

5-O-*Acetyl*-1 : 6-*di*-O-*benzoyl*-2 : 4-O-*methylene*-D-*glucitol*.—A solution of 5-*O*-acetyl-6-*O*-benzoyl-1 : 3-2 : 4-di-*O*-methylene-D-glucitol (0·20 g.) in benzoic acid (3 mol.) and trifluoroacetic anhydride (3 mol.) was kept at 25° for 12 hr., poured into sodium hydrogen carbonate solution, and extracted with chloroform. The dried ($MgSO_4$) extracts yielded a syrup, which crystallised from ethanol to give 5-*O*-acetyl-1 : 6-di-*O*-benzoyl-2 : 4-*O*-methylene-D-glucitol (0·16 g.), m. p. and mixed m. p. with the specimen obtained previously [2] 149—150°, $[\alpha]_D^{18}$ +5·9° (*c* 1·54 in $CHCl_3$) (Found: C, 62·0; H, 5·3. Calc. for $C_{23}H_{24}O_9$: C, 62·2; H, 5·4%).

Action of Benzoic Acid–Trifluoroacetic Anhydride on Tri-O-*methylene*-D-*glucitol*.—Tri-*O*-methylene-D-glucitol (0·50 g.) was kept at 25° for 12 hr. in a solution of benzoic acid (4·5 mol.) in trifluoroacetic anhydride (4·5 mol.). The mixture was worked up as before, to give 1 : 6-di-*O*-benzoyl-2 : 4-*O*-methylene-D-glucitol [2] (0·54 g.), m. p. and mixed m. p. 155—156° (from aqueous ethanol), $[\alpha]_D^{17}$ +16·9° (*c* 1·79 in $CHCl_3$) (Found: C, 62·7; H, 5·3; Bz, 52·2. Calc. for $C_{21}H_{22}O_6$: C, 62·7; H, 5·5; Bz, 52·2%).

Action of Propionic Acid–Trifluoroacetic Anhydride on Tri-O-*methylene*-D-*glucitol*.—A

[13] Hann, Wolfe, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 1898.
[14] Bourne and Wiggins, *J.*, 1944, 517.

solution of tri-*O*-methylene-D-glucitol (2·00 g.) in a mixture of trifluoroacetic anhydride (4·5 mol.) and propionic acid (4·5 mol.) was kept at 25° for 7 hr. Isolation of the product as before gave 2 : 4-O-*methylene*-1 : 6-*di*-O-*propionyl*-D-*glucitol* (2·01 g.) (from ethanol), m. p. 139—141°, $[\alpha]_D^{19}$ −4·8° (*c* 1·42 in $CHCl_3$) (Found: C, 50·9; H, 7·2; C_2H_5·CO, 36·8. $C_{13}H_{22}O_8$ requires C, 51·0; H, 7·2; C_2H_5·CO, 37·25%).

2 : 4-O-*Methylene*-D-*glucitol*.—2 : 4-*O*-Methylene-1 : 6-di-*O*-propionyl-D-glucitol (1·00 g.) was dissolved in dry methanol in which a small piece of sodium had been dissolved. After 24 hr. the methanol was removed by distillation and the residue recrystallised from ethanol, to give 2 : 4-*O*-methylene-D-glucitol (0·57 g.), m. p. and mixed m. p. 163—164°, $[\alpha]_D^{18}$ −9·1° (*c* 1·06 in H_2O) (Found: C, 43·6; H, 7·3. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·3%).

2 : 4-3 : 5-*Di*-O-*methylene*-1 : 6-*di*-O-*propionyl*-D-*glucitol*.—2 : 4-3 : 5-Di-*O*-methylene-D-glucitol (1·00 g.), prepared by the method of Hann *et al.*,[13] had m. p. 192—193°, $[\alpha]_D^{19}$ +40·7° (*c* 0·90 in H_2O). With propionic anhydride in pyridine it gave the 1 : 6-*dipropionate* (1·01 g.), m. p. 110—111° (from ethanol), $[\alpha]_D^{19}$ +3·6° (*c* 2·24 in $CHCl_3$) (Found: C, 52·9; H, 6·8; C_2H_5·CO, 35·5. $C_{14}H_{22}O_8$ requires C, 52·8; H, 7·0; C_2H_5·CO, 35·85%).

3 : 5-*Di*-O-*acetyl*-2 : 4-O-*methylene*-1 : 6-*di*-O-*propionyl*-D-*glucitol*.—(*a*) 2 : 4-*O*-Methylene-1 : 6-di-*O*-propionyl-D-glucitol (0·50 g.) with acetic anhydride in pyridine gave the 3 : 5-*di-acetate* (0·47 g.), m. p. 133—134° (from ethanol), $[\alpha]_D^{19}$ +1·7° (*c* 0·60 in $CHCl_3$) (Found: C, 52·5; H, 6·6. $C_{17}H_{26}O_{10}$ requires C, 52·3; H, 6·7%).

(*b*) A solution of 2 : 4-3 : 5-di-*O*-methylene-1 : 6-di-*O*-propionyl-D-glucitol (0·40 g.) in acetic acid (3 mol.) and trifluoroacetic anhydride (3 mol.) was kept at 25° for 7 hr. and poured into sodium hydrogen carbonate solution. The syrupy product, presumably 5-*O*-acetyl-2 : 4-*O*-methylene-1 : 6-di-*O*-propionyl-D-glucitol, was isolated by chloroform extraction. With acetic anhydride in pyridine it gave 3 : 5-di-*O*-acetyl-2 : 4-*O*-methylene-1 : 6-di-*O*-propionyl-D-glucitol (0·35 g.), m. p. 133—134° (from ethanol) alone and on admixture with specimen obtained in (*a*), $[\alpha]_D^{18}$ +1·5° (*c* 2·74 in $CHCl_3$).

Action of Acetic Acid–Trifluoroacetic Anhydride on Tri-O-*methylene*-D-*glucitol*.—(i) *Attempted preparation of* 1 : 6-*di*-O-*acetyl*-2 : 4-O-*methylene*-3 : 5-*bis*-O-*trifluoroacetoxymethyl*-D-*glucitol*. A solution of tri-*O*-methylene-D-glucitol (1·00 g.) in trifluoroacetic anhydride (4·5 mol.) and acetic acid (4·5 mol.) was kept at 25° for 7 hr. (constant rotation). Volatile material was removed at 15°/0·005 mm. A fluorine-containing syrup (2·10 g.), which smelled strongly of formaldehyde and trifluoroacetic acid, remained, and was probably impure 1 : 6-di-*O*-acetyl-2 : 4-*O*-methylene-3 : 5-bis-*O*-trifluoroacetoxymethyl-D-glucitol, b. p. 186—190°/0·02 mm. (Found: C, 41·5; H, 4·5. Calc. for $C_{17}H_{20}O_{12}F_6$: C, 38·5; H, 3·8%). Repeated attempts to obtain a pure compound failed and in every case the product smelled strongly of formaldehyde and trifluoroacetic acid.

(ii) 1 : 6-*Di*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*. Tri-*O*-methylene-D-glucitol (3·00 g.) was treated as in the previous experiment, but, after removal of the volatile products, the residual syrup was refluxed with dry methanol (25 ml.) for 1 hr. Evaporation of the methanol left a syrup which was 1 : 6-*di*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol* (3·18 g.), b. p. 167—168°/0·01 mm., $[\alpha]_D^{14}$ −1·5° (*c* 1·96 in acetone) (Found: C, 47·8; H, 6·5; Ac, 30·9. $C_{11}H_{18}O_8$ requires C, 47·5; H, 6·5; Ac, 30·9%). This had still not crystallised after 12 months.

(iii) 3 : 5-*Di*-O-*acetoxymethyl*-1 : 6-*di*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*. Tri-*O*-methylene-D-glucitol (1·0 g.) was kept at 60° for 6 hr. in trifluoroacetic anhydride (4·5 mol.) and acetic acid (45 mol.), poured into sodium hydrogen carbonate solution and extracted with chloroform. The product was 3 : 5-di-*O*-acetoxymethyl-1 : 6-di-*O*-acetyl-2 : 4-*O*-methylene-D-glucitol (1·31 g.), m. p. and mixed m. p. 110—111° (from ethanol), $[\alpha]_D^{14}$ +26·9° (*c* 2·31 in $CHCl_3$). Ness *et al.*[3] gave m. p. 111—112° and $[\alpha]_D$ +29·8° (in $CHCl_3$).

1 : 3 : 5 : 6-*Tetra*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol from* 1 : 6-*Di*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*.—The diacetate (0·50 g.) with acetic anhydride in pyridine gave the tetra-acetate (0·54 g.), m. p. and mixed m. p. 150—151° (from aqueous ethanol), $[\alpha]_D^{17}$ −2·0° (*c* 2·03 in $CHCl_3$) (Found: C, 49·8; H, 6·0%).

Methylation of 1 : 6-*Di*-O-*acetyl*-2 : 4-O-*methylene*-D-*glucitol*.—The diacetate (2·00 g.) was refluxed for 24 hr. with methyl iodide (40 ml.) and silver oxide (16·0 g.). The solvent was distilled, the residue was extracted with boiling chloroform, the filtered extracts were evaporated, and the residue was remethylated twice more in the same way. The *dimethyl ether* (1·31 g.) was a syrup, b. p. 158—164°/0·02 mm., $[\alpha]_D^{15}$ +4·2° (*c* 2·17 in $CHCl_3$) (Found: C, 50·6; H, 7·0; Ac, 27·7; OMe, 20·7. $C_{13}H_{22}O_8$ requires C, 51·0; H, 7·2; Ac, 28·1; OMe, 20·3%).

Action of Acetic Acid–Trifluoroacetic Anhydride on 3 : 4-*Di*-O-*acetyl*-1 : 2-5 : 6-*di*-O-iso*propylidene*-D-*mannitol*.—A solution of the compound (0·50 g.) {m. p. 123° and $[\alpha]_D^{17}$ +25·1° (*c* 1·92 in $CHCl_3$); Vargha [15] gave m. p. 123° and $[\alpha]_D$ +26·7° (in $CHCl_3$)} in acetic acid (6 mol.) and trifluoroacetic anhydride (6 mol.) was kept at 25°. After 2 hr. it had become almost black; it was poured into sodium hydrogen carbonate solution and extracted with chloroform. The extracts were dried ($MgSO_4$), decolorised with charcoal, filtered, and evaporated. The residue yielded D-mannitol hexa-acetate (21%), m. p. and mixed m. p. 122°, $[\alpha]_D^{21}$ + 25·0° (*c* 2·32 in $CHCl_3$).

1 : 3 : 5 : 6-*Tetra*-O-*acetyl*-2 : 4-O-*benzylidene*-D-*glucitol*.—2 : 4-*O*-Benzylidene-D-glucitol [16] (1·00 g.) with acetic anhydride in pyridine gave the *tetra-acetate* (1·22 g.), m. p. 121°, $[\alpha]_D^{20}$ −5·2° (*c* 1·49 in $CHCl_3$) (Found: C, 57·6; H, 5·9; Ac, 39·8. $C_{21}H_{26}O_{10}$ requires C, 57·5; H, 6·0; Ac, 39·3%).

De-acetylation of 1 : 3 : 5 : 6-*Tetra*-O-*acetyl*-2 : 4-O-*benzylidene*-D-*glucitol*.—The compound (0·50 g.) was dissolved in dry methanol in which a small piece of sodium had been dissolved. Evaporation of the methanol after 17 hr. left a solid which gave 2 : 4-*O*-benzylidene-D-glucitol (0·28 g.), m. p. and mixed m. p. 175—176° (from aqueous ethanol), $[\alpha]_D^{16}$ +7·9° (*c* 0·76 in ethanol).

Action of Acetic Acid–Trifluoroacetic Anhydride on Benzylidene Acetals.—(a) *Tri*-O-*benzylidene*-D-*mannitol*. (i) A solution of the compound (0·50 g.), prepared by Pette's method [17] {m. p. 212—216°, $[\alpha]_D^{17}$ −15·0° (*c* 2·30 in $CHCl_3$); Pette gave m. p. 224°}, in acetic acid (24 mol.) and trifluoroacetic anhydride (24 mol.) was kept at 25° for 24 hr. Considerable darkening took place. The mixture was poured into sodium hydrogen carbonate solution. The product, isolated by chloroform-extraction, was D-mannitol hexa-acetate (39%), m. p. and mixed m. p. 122—123°, $[\alpha]_D^{17}$ +24·2° (*c* 0·91 in $CHCl_3$).

(ii) The reaction was carried out as in (*a*) but, instead of being poured into sodium hydrogen carbonate solution, the reaction mixture was distilled. The distillate was taken up in chloroform, washed with sodium hydrogen carbonate solution and water, and dried ($MgSO_4$). Evaporation of the chloroform left a liquid which smelled strongly of benzaldehyde and did not contain fluorine. This was converted into benzaldehyde 2 : 4-dinitrophenylhydrazone (73%), m. p. and mixed m. p. 237°.

(b) 1 : 3 : 5 : 6-*Tetra*-O-*acetyl*-2 : 4-O-*benzylidene*-D-*glucitol*. A solution of this compound (0·50 g.) in acetic acid (8 mol.) and trifluoroacetic anhydride (8 mol.) was treated as in the previous experiment, to give D-glucitol hexa-acetate (85%), m. p. and mixed m. p. 99·5—100°, $[\alpha]_D^{17}$ +8·2° (*c* 5·40 in acetone), and benzaldehyde 2 : 4-dinitrophenylhydrazone (74%), m. p. and mixed m. p. 237°.

Acetylation of Acetals and Ketals with Acetic Acid–Trifluoroacetic Anhydride.—1 : 3-2 : 4-Di-*O*-methylene-D-glucitol, 1 : 3-2 : 4-di-*O*-ethylidene-D-glucitol, and 2 : 4-*O*-benzylidene-D-glucitol were fully acetylated in 68%, 59%, and 64% yield, respectively, by the following method: the acetal (0·50 g.) was dissolved in acetic acid (1·2 mol. per hydroxyl group) and trifluoroacetic anhydride (1·2 mol. per hydroxyl group), and the solution kept at room temperature for about 20 hr. The reaction mixture was taken up in chloroform, washed with sodium hydrogen carbonate solution, and water, and dried ($MgSO_4$). Evaporation of the chloroform and recrystallisation of the product from ethanol gave the required acetate. 1 : 2-5 : 6-Di-*O*-*iso*propylidene-D-mannitol gave a yield of less than 10%, and 1 : 2-5 : 6-di-*O*-*iso*propylidene-D-glucitol no yield of the corresponding acetate by this method.

Non-reactivity of Acetyl Trifluoroacetate with Cyclic Acetals.—When treated with acetyl trifluoroacetate (1 mol.), 1 : 6-di-*O*-benzoyl-2 : 4-3 : 5-di-*O*-methylene-D-glucitol (0·17 mol., 3 hr. at 25°), tri-*O*-methylene-D-glucitol (0·10 mol., 7 hr. at 25°), tri-*O*-benzylidene-D-mannitol (0·02 mol., 24 hr. at 25°), and 1 : 3 : 5 : 6-tetra-*O*-acetyl-2 : 4-*O*-benzylidene-D-glucitol (0·06 mol., 24 hr. at 25°) were recovered unchanged (yields 88, 62, 64, and 86%, respectively).

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[15] Vargha, *Ber.*, 1933, **66**, 1394.
[16] Angyal and Lawler, *J. Amer. Chem. Soc.*, 1944, **66**, 837.
[17] Pette, *Ber.*, 1931, **64**, 1567.

371. *Homolytic Aromatic Substitution. Part XVII.* The Phenylation of Tritiobenzene.*

By Chang Shih, D. H. Hey, and Gareth H. Williams.

Phenylation of tritiated benzene with benzoyl peroxide has been shown not to involve a kinetic isotope effect. The substitution stage of this reaction is therefore considered to proceed by slow formation of an addition complex between the phenyl radical and the substrate, followed by loss of a hydrogen atom, probably as a result of interaction of the complex with another radical or other oxidising agent in a fast, kinetically insignificant, stage.

Three mechanisms may be suggested for the substitution step in homolytic arylation. These are:

(*a*) Removal of a hydrogen atom from a substrate molecule by the attacking phenyl radical, leaving an aryl radical, which eventually combines with another aryl radical to yield a diaryl:

$$ArH + Ph^{\bullet} \longrightarrow Ar^{\bullet} + PhH$$
$$Ar^{\bullet} + Ar^{\bullet} \text{ (or } Ph^{\bullet}) \longrightarrow Ar_2 \text{ (or ArPh)}$$

(*b*) Synchronous approach of the attacking phenyl radical and recession of the ejected hydrogen atom:

$$Ph^{\bullet} + ArH \longrightarrow \left[Ar\begin{matrix} Ph \\ H \end{matrix} \right]^{\bullet} \longrightarrow ArPh + H^{\bullet}$$

(*c*) Slow formation of an addition complex between the phenyl radical and substrate, followed by the loss of a hydrogen atom, probably by interaction with another radical or other oxidising agent, in a fast, kinetically insignificant stage:

$$Ph^{\bullet} + ArH \xrightarrow[\text{Slow}]{} \left[Ar\begin{matrix} Ph \\ H \end{matrix} \right]^{\bullet} \xrightarrow[\text{Fast}]{(R^{\bullet})} ArPh + H^{\bullet}\ (RH)$$

The first mechanism has been discussed by Grieve and Hey [1] and by Hey and Waters [2] and, more recently, by Augood, Hey, and Williams [3] and by Augood and Williams,[4] and was considered unlikely. The second and the third mechanism differ from mechanism (*a*) in that they represent reactions of hydrogen replacement rather than of hydrogen abstraction. These two mechanisms (*b*) and (*c*) were discussed by Augood and Williams [4] who concluded that mechanism (*c*) was the more likely, a view which had been previously put forward by Price [5] and by Hey, Nechvatal, and Robinson.[6] This mechanism can involve, as a non-kinetically significant stage, either the ejection of a free hydrogen atom or its removal by another radical. The latter alternative has always been favoured in preference to the former (see, for example, Hey, Nechvatal, and Robinson [6]), and this view was accepted by Augood and Williams.[4] However, this conclusion has been misinterpreted by Lewis and Symons [7] who, in a brief and incomplete discussion of the subject, attributed the opposite view to Augood and Williams, and themselves restated the actual views of those authors. The confusion has arisen from the quotation by Lewis and Symons of

* Part XVI, *J.*, 1958, 4403.

[1] Grieve and Hey, *J.*, 1934, 1797.
[2] Hey and Waters, *Chem. Rev.*, 1937, **21**, 169.
[3] Augood, Hey, and Williams, *J.*, 1952, 2094.
[4] Augood and Williams, *Chem. Rev.*, 1957, **57**, 123.
[5] Price, "Reactions at the Carbon–Carbon Double Bond," Interscience Publ. Inc., New York, 1946.
[6] Hey, Nechvatal, and Robinson, *J.*, 1951, 2892.
[7] Lewis and Symons, *Quart. Rev.*, 1958, **12**, 230.

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equation (1) from Augood and Williams's review [4] as an expression of the reaction mechanism, whereas it was employed by Augood and Williams merely as a means of distinguishing the stoicheiometry of hydrogen replacement by mechanisms (*b*) and (*c*) from that of hydrogen abstraction by mechanism (*a*).

$$C_6H_5X + C_6H_5\cdot \longrightarrow C_6H_5\cdot C_6H_4X + H\cdot \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Of mechanisms (*b*) and (*c*), only (*b*) should be subject to a kinetic isotope effect. This test has been applied by Milyutinskaya, Bagdasaryan, and Izrailevich [8] to the arylation of some deuterated aromatic compounds by measurement of the deuterium content of the diaryls, and by Convery and Price [9] to the phenylation of 2 : 4-dinitrotritiobenzene. No isotope effect was found in either investigation. However, it appears desirable to apply this test to the simplest possible arylation, namely, the phenylation of benzene, using the conditions most favourable to the exhibition of an isotope effect of appreciable magnitude.

The radical R·, which is responsible for bringing about the second stage of mechanism (*c*), is usually the benzoyloxy-radical. However, it has been shown that under certain circumstances the radical R· can be a second aryl*cyclo*hexadienyl radical (the addition complex formed in the first stage). The interaction of two such radicals may then give rise by disproportionation to the formation of one molecule of a diaryl and one molecule of a dihydrodiaryl, which may subsequently become oxidised to a diaryl. De Tar and Long [10] have thus isolated a dihydrodiphenyl after decomposition of benzoyl peroxide in very dilute solution in benzene under nitrogen. If some of the diaryl is formed in this way, even under less extreme conditions, its isotopic composition can clearly not be independent of the relative rates of removal of hydrogen and tritium from the addition complex, and the measurement of the isotopic composition of the diaryl is not strictly diagnostic of the existence or non-existence of an isotope effect in the formation of the complex. However, the isotopic composition of the unchanged aromatic substrate is dependent only on the formation of addition complexes, and should be different from the isotopic composition of the starting material only if the formation of the complex, or transition state, involves partial cleavage of the C–H bond [mechanism (*b*) above]. The magnitude of the expected change in isotopic composition can be appreciable provided the initial concentration of benzoyl peroxide in tritiobenzene is high.

Our results show that the isotopic composition of the substrate is unchanged within experimental error. The maximum possible error in the determinations was estimated to be $\pm 3\%$, since a number of specimens of tritiated benzene were assayed to this degree of accuracy. The actual error is probably smaller than this. Thus, the ratio of the final to the initial activity must be less than 1·03, and calculations show that the ratio of the rates of reaction at carbon atoms carrying hydrogen and tritium respectively (k_H/k_T) cannot therefore be greater than 1·2. Isotope effects with tritium, if they operate at all, are expected to be much greater (cf. Bigeleisen [11]). Hence one may conclude that the contribution of energy associated with the partial cleavage of the C–H or C–T bond can make, at most, only a very small contribution to the activation energy for the substitution reaction, and that therefore mechanism (*c*) is a much more accurate picture of the process than mechanism (*b*).

Experimental

Tritiated benzene was prepared by the exchange reaction of benzene with tritiated aqueous sulphuric acid.[12] Benzene (24 ml.) was shaken at room temperature for 4 days with tritiated 83% w/w sulphuric acid (10 ml.). After separation from the acid, the benzene was washed twice with water, then with aqueous sodium carbonate, and with water again. After being

[8] Milyutinskaya, Bagdasaryan, and Izrailevich, *Zhur. fiz. Khim.*, 1957, **31**, 1019
[9] Convery and Price, *J. Amer. Chem. Soc.*, 1958, **80**, 4101.
[10] De Tar and Long, *ibid.*, p. 4742.
[11] Bigeleisen, Brookhaven Conference Report, Isotopic Exchange Reactions and Chemical Kinetics, 1948, p. 53.
[12] Ingold and Wilson, *J.*, 1936, 915.

dried ($CaCl_2$) it was twice distilled through an 8″ helix-packed column (b. p. 79·5°, n_D^{20} 1·5008). It was diluted with inactive benzene to the required activity. At the tracer level of activity, at which it was prepared, the mole fraction of C_6H_5T is of the order of 10^{-6}, so that the concentration of doubly tritiated molecules ($C_6H_4T_2$) is quite negligible.

Reaction of Benzoyl Peroxide with Tritiated Benzene.—In experiments 1 and 2, benzoyl peroxide (6 g.) was allowed to decompose in tritiated benzene (20 ml. and 12 ml. respectively) for 24 hr. at 80° (thermostat). In experiment 3, benzoyl peroxide (30 g.) was allowed to decompose in tritiated benzene (20 ml.) under the same conditions. The residual tritiated benzene was then collected by careful distillation through a helix-packed column at atmospheric pressure. It was redistilled once and analysed for tritium activity by gas counting. The percentage conversion of tritiated benzene was 11, 18, and 55 in the three experiments.

Assay of Tritiated Benzene.—Through a vacuum line of standard design, the tritiated benzene was introduced into a gas counter (type GA 10/M) at known pressure, together with the basic filling gas, which for the present determinations was butane.[13] The tritiated benzene formed 10—30% of the gas mixture. Under these conditions it had previously been found possible to count the tritiated benzene with a reproducibility better than ±3% in the Geiger region. The length of the plateau was about 200 v and its slope rather less than 3% per 100 v. Before each determination, the counter-tube was heated in a stream of warm air and pumped out continuously. It was then filled with pure butane for the determination of the background counting rate. After this determination, it was flushed with a mixture of the required composition and again filled for the determination of the activity of the tritiated benzene. The results of experiments 1, 2, and 3 are summarised in the Table, which shows that, within the experimental error, the activity of the tritiated benzene is unchanged after reaction with benzoyl peroxide.

Experiment no.		1	2	3
Sp. activity (c.p.m./ml.*):	original benzene	499	499	1298
,, ,, ,, ,,	residual ,,	496 †	505	1271

* At S.T.P. † Counted after dilution to twice its volume with inactive benzene, in order to check the results and eliminate the possibility of coincidence.

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STRAND, LONDON, W.C.2. [*Received, January 9th,* 1959.]

[13] Powell and Reid, *J. Amer. Chem. Soc.*, 1945, **67**, 1020.

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372. *Molecular Rearrangements. Part III.* The Thermal Rearrangement of Aryl Benzyl Ethers.*

By F. M. ELKOBAISI and W. J. HICKINBOTTOM.

When purified benzyl phenyl ether is heated at about 250° for some days, it rearranges to give *o*- and *p*-benzylphenols and 2 : 4-dibenzylphenol, together with phenol, toluene, and 9-phenylxanthen.

o- and *p*-Tolyl, 2 : 4-dimethylphenyl, and 2 : 6-dimethylphenyl benzyl ethers similarly rearrange and also yield toluene and the corresponding xanthen.

The rearrangement is not proton-catalysed: it is essentially a migration of the benzyl group brought about by heating to a sufficiently high temperature.

BENZYL PHENYL ETHER was reported by Powell and Adams [1] to change slowly on heating under reflux to toluene, phenol, and unidentified high-boiling material. Behagel and Freiensehner [2] found that by longer boiling some *p*-benzylphenol was formed as well as

* Part II, *J.*, 1958, 2982.

[1] Powell and Adams, *J. Amer. Chem. Soc.*, 1920, **42**, 656.
[2] Behagel and Freiensehner, *Ber.*, 1934, **67**, 1368.

phenol and some high-boiling products. The formation of benzylphenols occurred more readily if zinc were present. Other aryl benzyl ethers also rearrange under similar condition.

It appeared possible that these migrations are proton-catalysed as a result of hydrolysis of traces of benzyl chloride by moisture. If this were so, the action of zinc in accelerating the change can be explained simply and rationally in terms of known observation.[3] Support for this view is provided by the observation that benzyl chloride is often a persistent impurity in benzyl phenyl ether as ordinarily prepared.

A method of preparing benzyl phenyl ether very pure and free from traces of benzyl chloride has been developed. Using it we have established that it decomposes when heated at its boiling point: after about 20 hours toluene, phenol, and benzaldehyde are obtained in small yields together with some *p*-benzylphenol. More complete rearrangement is brought about by heating in sealed tubes for some days at 250°; *o*- and *p*-benzylphenols are formed together with phenol, toluene, 2 : 4-dibenzylphenol, and 9-phenylxanthen. The benzyl ethers of *o*- and *p*-cresol, of 2 : 4- and 2 : 6-dimethylphenol, and of *p*-chlorophenol similarly rearrange to form toluene, the phenol, and a substituted 9-phenylxanthen.

The production of toluene and 9-phenylxanthen distinguishes this rearrangement from that induced by proton catalysis or Lewis acids. There can be little doubt that this is a thermal isomerisation of the same type, although not necessarily the same mechanism as the Claisen rearrangement of allyl aryl ethers.

Experimental

Preparation of Aryl Benzyl Ethers.—All ethers were prepared by refluxing benzyl chloride with a slight excess (1·1 moles) of the appropriate phenol in acetone containing an excess of finely powdered potassium carbonate in suspension.

To ensure the absence of traces of benzyl chloride, the crude redistilled ether was heated under reflux with dry pyridine for some hours. The ether was recovered by dilution with water; the oil which separated was taken up in ether and freed from pyridine by repeated washing with dilute hydrochloric acid. After a final treatment with sodium hydroxide solution, the dried ethereal solution was distilled, and the whole process of purification repeated on the aryl benzyl ether until there was no detectable trace of chloride in the product.

Thermal Rearrangement of Aryl Benzyl Ethers.—Benzyl phenyl ether: (a) *Under reflux.* Benzyl phenyl ether (50 g., m. p. 42°) was boiled under reflux. The temperature of the boiling liquid fell from 270° to 250° during the first 3 hr. and remained thereat. The colour changed through pale yellow to dark brown as the heating continued. After 20 hours' heating the liquid was distilled, first at atmospheric pressure up to 200° and thereafter under reduced pressure. There were obtained (*a*) water (0·5 g.), (*b*) toluene [2·8 g. (2 : 4-dinitro-derivative, m. p. and mixed m. p. 72°)], (*c*) benzaldehyde [0·8 g. (2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 158°)], (*d*) phenol, m. p. 42° (5·5 g.), (*e*) benzyl phenyl ether, b. p. 130—150°/14 mm. (26·5 g.) (after crystallisation from alcohol this fraction melted at 42°), (*f*) *p*-benzylphenol (1·8 g.), m. p. 84° after crystallisation from alcohol, unchanged by admixture with an authentic sample. A tar (10 g.) remained which did not give recognisable components.

(b) *In sealed tubes.* Benzyl phenyl ether (70 g.) become thick and dark brown with a greenish fluorescence after it had been heated at 250° for 7 days in sealed tubes; it also had a pronounced phenolic odour.

The lower-boiling fractions (b. p. up to 200°) from the rearrangement product were separated into water (1·5 g.), toluene (10 g.), and phenol (2·6 g.). The higher-boiling material was separated into neutral (*A*) and phenolic (*B*) products by extraction with Claisen's solution [4] after dilution with ether and light petroleum.

From the neutral matter there was separated, by distillation, benzyl phenyl ether (10·2 g.) and a fraction of b. p. 220—240°/14 mm. (16·5 g.) which became semisolid on cooling. By trituration with alcohol and crystallisation from the same solvent the main constituent was

[3] (*a*) Von Alphen, *Rec. Trav. chim.*, 1927, **46**, 804; (*b*) Short, *J.*, 1928, 528; (*c*) Short and Stewart, *J.*, 1929, 558.

[4] Claisen, *Annalen*, 1925, **442**, 224, footnote.

obtained pure, m. p. 145° (Found: C, 87·9; H, 5·4. Calc. for $C_{19}H_{14}O$: C, 88·3; H, 5·4%). It dissolved in concentrated sulphuric acid with development of a yellow colour and it was identified as 9-phenylxanthen by comparison with an authentic specimen prepared from xanthone and phenylmagnesium bromide with subsequent reduction of the 9-phenylxanthhydrol by zinc and platinum chloride in aqueous acetic acid.[5]

The phenolic products of the rearrangement were separated by distillation into (*a*) phenol (1·1 g.), (*b*) crude *o*-benzylphenol, b. p. 170—180°/14 mm. (2·2 g.), (*c*) crude *p*-benzylphenol, b. p. 180—200°/14 mm. (5·0 g.), and (*d*) 2 : 4-dibenzylphenol, b. p. 260—270°/14 mm. (0·4 g.).

o-Benzylphenol was characterised by its phenylurethane, m. p. and mixed m. p. 117°; *p*-benzylphenol was obtained solid and after crystallisation had m. p. 84°, not depressed by admixture with an authentic specimen (Found: C, 87·6; H, 6·8. Calc. for $C_{13}H_{12}O$: C, 87·6; H, 6·6%); 2 : 4-dibenzylphenol after crystallisation had m. p. and mixed m. p. 48—49° (Found: 84·9; H, 6·6. Calc. for $C_{20}H_{18}O$: C, 84·8; H, 6·6%) (α-naphthylurethane, m. p. and mixed m. p. 114°).

Benzyl o-tolyl ether. This ether (b. p. 158°/14 mm.; Schorigin[6] gives b. p. 284° or 183°/24 mm.) does not rearrange readily on boiling under reflux. When it was heated in sealed tubes for 10 days at 250°, water (2·2 g.), toluene (18·5 g.), and *o*-cresol, m. p. 30° (31 g.), were obtained from 130 g. of ether.

The neutral components of the rearrangement product were unchanged ether (20 g.) and 4 : 5-*dimethyl*-9-*phenylxanthen* (20 g.), b. p. 240—260°/18 mm., m. p. 120° after crystallisation from alcohol (Found: C, 88·2; H, 6·4. $C_{21}H_{18}O$ requires C, 88·0; H, 6·3%).

The phenolic components were separated by careful fractionation into 2-benzyl-6-methylphenol, b. p. 137—140°/1 mm., m. p. and mixed m. p. 50·5° (Found: C, 84·7; H, 7·0. Calc. for $C_{14}H_{14}O$: C, 84·8; H, 7·1%) (4-bromo-derivative, m. p. and mixed m. p. 64°); 4-benzyl-2-methylphenol, b. p. 140—150°/0·8 mm., m. p. and mixed m. p. 49·5° (Found: C, 84·9; H, 7·0%) (benzoate, m. p. and mixed m. p. 55°), and an orange oil, b. p. 210°/0·8 mm. (Found: C, 87·3; H, 7·0. Calc. for $C_{21}H_{20}O$: C, 87·45; H, 7·0%). It is indifferent to bromine and is presumably 2 : 4-dibenzyl-6-methylphenol. The total weight of these phenols was 14·2 g. of which about 1/5 was the last and the remainder approximately equal weights of the benzyl-*o*-cresols.

For comparison 4-benzyl-2-methyl phenol[7] was prepared by adding aluminium chloride (65 g.) to *o*-cresol (100 g.) and benzyl alcohol (100 g.) in light petroleum (200 g.), the temperature being kept at 30—35°. Next morning evolution of hydrogen chloride had ceased; it was then decomposed and 4-benzyl-2-methylphenol isolated by distillation, b. p. 185°/13 mm., m. p. 49° (benzoate, m. p. 55°).

Preparation of 4 : 5-*Dimethyl*-9-*phenylxanthen.*—4 : 5-Dimethylxanthone, m. p. 170°, was prepared in relatively poor yield from 2-hydroxy-3-methylbenzoic acid by boiling it with acetic anhydride and then distilling.[8]

By reaction with phenylmagnesium bromide in ether, 4 : 5-dimethyl-9-phenylxanthhydrol was obtained, yellow prisms from light petroleum (b. p. 60—80°), m. p. 137°. It was reduced by zinc dust in acetic acid to which a few drops of platinic chloride had been added. There resulted 4 : 5-dimethyl-9-phenylxanthen (colourless needles from alcohol), m. p. 117—117·5°, not depressed by admixture with that isolated from the rearrangement product.

Thermal Rearrangement of Aryl Benzyl Ethers.—Benzyl p-*tolyl ether.* The purified ether (70 g., m. p. 40°; Claisen[9] gives m. p. 41°; Baw,[10] m. p. 40°), heated under reflux for 40 hr., gave water (0·6 g.), toluene (3·8 g.), *p*-cresol (11·5 g.), unchanged ether (25 g.), 2-benzyl-4-methylphenol (4·0 g.), 2 : 7-dimethyl-9-phenylxanthen (4·0 g.), and a tar (12 g.).

When the ether (90 g.) was heated in sealed tubes at 280° for 14 days, the following products were obtained: water (1·0 g.), toluene (16·6 g.), *p*-cresol (14 g.), 2-benzyl-4-methylphenol (10·5 g.), 2 : 7-dimethyl-9-phenylxanthen (23·5 g.), and a tar (10 g.).

2-Benzyl-4-methylphenol was identified by comparison with an authentic sample,[11] m. p. and mixed m. p. 36° (Found: C, 84·2; H, 7·1%), and by its phenylurethane, m. p. and mixed m. p. 146°.

[5] Ullman and Engi, *Ber.*, 1904, **37**, 2370.
[6] Schorigin, *Ber.*, 1925, **58**, 2032, footnote 14.
[7] Huston, *J. Amer. Chem. Soc.*, 1930, **52**, 4486.
[8] Schopfi, *Ber.*, 1892, **25**, 3647.
[9] Claisen, *Annalen*, 1925, **442**, 242.
[10] Baw, *Quart. J. Indian Chem. Soc.*, 1926, **3**, 101.
[11] Elkobaisi and Hickinbottom, *J.*, 1958, 2431.

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2 : 7-Dimethyl-9-phenylxanthen, m. p. 195° from alcohol (Found: C, 88·0; H, 6·5%), gives a yellow colour with concentrated sulphuric acid. It was identical with the product obtained by distilling 2 : 2′-dihydroxy-5 : 5′-dimethyltriphenylmethane.[12]

Benzyl 2 : 4-*dimethylphenyl ether*. This is a somewhat viscous faint yellow *liquid*, b. p. 180°/15 mm. (Found: C, 84·9; H, 7·5. $C_{15}H_{18}O$ requires C, 84·9; H, 7·6%). Heated in sealed tubes at 270° for 17 days, 70 g. of it gave water (1·3 g.), toluene (12·0 g.), 2 : 4-dimethylphenol (11·5 g.), 6-benzyl-2 : 4-dimethylphenol (18 g.), and 2 : 4 : 5 : 7-tetramethyl-9-phenylxanthen (12 g.).

6-Benzyl-2 : 4-dimethylphenol, m. p. 67° (Found: C, 84·6; H, 7·7. Calc. for $C_{15}H_{16}O$: C, 84·9; H, 7·6%) (phenylurethane, m. p. 138°), was identical (mixed m. p.) with a sample prepared in another way.[10]

2 : 4 : 5 : 7-*Tetramethyl-9-phenylxanthen*, colourless prisms, m. p. 108° (Found: C, 87·9; H, 7·1. $C_{23}H_{22}O$ requires C, 87·9; H, 7·1%), gives an orange-yellow colour with concentrated sulphuric acid.

Benzyl 2 : 6-*dimethylphenyl ether*.[13] This, b. p. 162°/14 mm. (Found: C, 84·8; H, 7·6%), was heated at 260° for 14 days. From 106 g. of ether there were obtained water (1·8 g.), toluene (21·4 g.), 2 : 6-dimethylphenol (20 g.), 4-benzyl-2 : 6-dimethylphenol (27 g.), and an unidentified product, b. p. 234—250°/14 mm. (18 g.).

4-Benzyl-2 : 6-dimethylphenol, b. p. 190—196°/14 mm., m. p. 66° (Found: C, 84·3; H, 7·8%) (phenylurethane, m. p. 153°), was identified by comparison with an authentic sample prepared by reaction of 2 : 6-dimethylphenol with benzyl alcohol and aluminium chloride in light petroleum at 30—35°. Two main products were isolated, 4-benzyl-2 : 6-dimethylphenol, b. p. 196°/14 mm., m. p. 66° not depressed by admixture with that isolated from the rearrangement (Found: C, 84·5; H, 7·7%), and its benzyl ether, m. p. 118°, needles from light petroleum.

Benzyl 4-*chlorophenyl ether*. By refluxing this ether (40 g.) for 12 hr. there were obtained water (0·3 g.), toluene (2·9 g.), *p*-chlorophenol (7·7 g.), 2-benzyl-4-chlorophenol (7·5 g.), and 2 : 7-dichloro-9-phenylxanthen (1·5 g.); a dense black tar (17 g.) remained.

The ether (60 g.), heated in sealed tubes for 9 days at 260°, gave toluene (2·1 g.), *p*-chlorophenol (14·1 g.), unchanged ether (0·7 g.), 2-benzyl-4-chlorophenol (12·6 g.), 2 : 7-dichloro-9-phenylxanthen (15·8 g.), and tar (15 g.).

2-Benzyl-4-chlorophenol, m. p. 53° (Found: C, 71·4; H, 4·95; Cl, 16·1. Calc. for $C_{13}H_{11}OCl$: C, 71·4; H, 5·0; Cl, 16·2%), is identical with that prepared in another way.

2 : 7-*Dichloro-9-phenylxanthen* had m. p. 195° (from acetic acid) (Found: C, 70·0; H, 3·4; Cl, 21·4. $C_{19}H_{12}OCl_2$ requires C, 69·7; H, 3·7; Cl, 21·7%).

Benzyl 4-chlorophenyl ether had b. p. 180—182°/mm., m. p. 71—72° (Baw [10] gives m. p. 71°) (Found: C, 71·2; H, 5·0; Cl, 16·6. Calc. for $C_{13}H_{11}OCl$: C, 71·4; H, 5·0; Cl, 16·2%).

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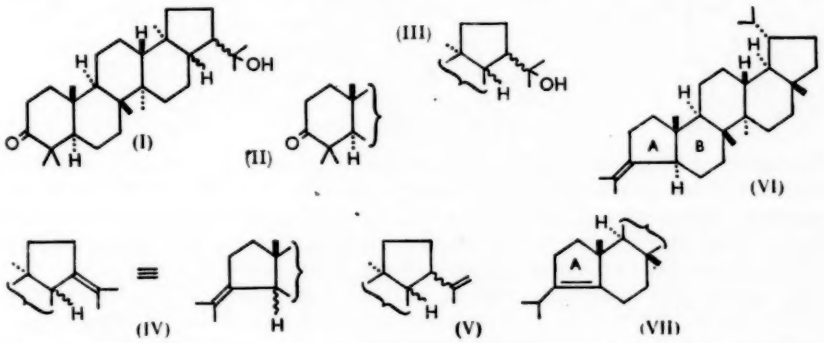
[12] Feuerstein and Lipp, *Ber.*, 1902, **35**, 3252.
[13] Curtin, *J. Amer. Chem. Soc.*, 1958, **80**, 1397.

373. *The Chemistry of Triterpenes and Related Compounds. Part XXXIV.* The Structure of Hydroxyhopanone.*

By H. Fazakerley, T. G. Halsall, and E. R. H. Jones.

The structure (I) suggested [1] for hydroxyhopanone [2] has been confirmed by a study of the products of acid-catalysed isomerisation of hopenone. One of these, hopenone-I (VIII), has been prepared from γ-onocerin by Jeger and his co-workers.[3] Hydroxyhopanone is one of the few pentacyclic triterpenes biosynthesised from squalene without rearrangement of the carbon skeleton.

Structure (I) has recently been suggested [1] for hydroxyhopanone,[2] which was shown to include the structural features (II) and (III).[1] Dehydration of hydroxyhopanone with phosphoryl chloride in pyridine yielded hopenone, a mixture of the *iso*propylidene and *iso*propenyl isomers, hopenone-a (IV) and hopenone-b (V). Structure (IV) is similar to



that of γ-lupene [4] (VI) which is isomerised by acid to *iso*-γ-lupene (VII),[5,6] and in the expectation of obtaining further information about rings D and E in hydroxyhopanone acid-catalysed isomerisations were studied.

A new ketone, hopenone-I, crystallised immediately from the mixture when hopenone was treated with 8% sulphuric acid in acetic acid. A similar result was obtained with the parent hydroxyhopanone. The mother liquors from these reactions contained a lower-melting isomer, hopenone-II, which was obtained more conveniently by treating hopenone-I with 15% sulphuric acid in acetic acid. Wolff–Kishner reduction of hopenone-I gave hopene-I and from hopenone-II hopene-II was obtained with another compound (probably a hydrocarbon) which has not yet been investigated further. Hopene-II was also obtained directly by isomerisation of hopene.

The infrared spectra of hopenone-I and -II and of hopene-I and -II indicated the absence of a di- or tri-substituted double bond and it was concluded that the double bond in each compound was tetrasubstituted. The ultraviolet absorption properties are compared with those of appropriate standard substances in Table 1. The end absorption of hopenone-I and hopene-I resembles that of *iso*-γ-lupene (VII) whilst that of hopenone-II

* Part XXXIII, *J.*, 1958, 2603.

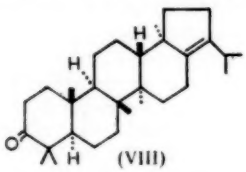
[1] Dunstan, Fazakerley, Halsall, and Jones, *Croat. Chim. Acta*, 1957, **29**, 173; cf. *Proc. Chem. Soc.*, 1957, 228.
[2] Mills and Werner, *J.*, 1955, 3132.
[3] Schaffner, Caglioti, Arigoni, and Jeger, *Helv. Chim. Acta*, 1958, **41**, 152.
[4] Heilbron, Kennedy, and Spring, *J.*, 1938, 329.
[5] Nowak, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 323.
[6] Barton, de Mayo, and Orr, *J.*, 1958, 2239.

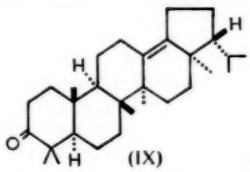
and hopene-II is similar to that of δ-amyrenone [7] which consists predominantly of olean-13(18)-en-3-one (85%), with a tetrasubstituted doubly exocyclic double bond, along with 18α-olean-12-en-3-one.[8]

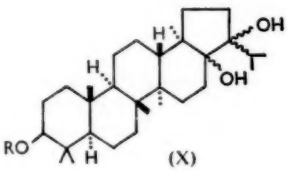
TABLE 1. *Values of* $\varepsilon_{obs.}$ *in alcohols.*

	2100 Å	2150 Å	2200 Å	$\varepsilon_{2100}/\varepsilon_{2200}$
Hopenone-I (VIII)	6250	3480	1700	3·6
Hopene-I	6950	4180	2200	3·2
iso-γ-Lupene (VII)	4950	3000	1450	3·4
Hopenone-II (IX)	9350	6050	3850	2·4
Hopene-II	8100	5700	3300	2·4
δ-Amyrenone	6220	4700	3590	1·7

The most likely structures for hopenone-I and hopenone-II appeared to be (VIII) and (IX) although the possibility of ring E enlargement as in the sequence lupenone ⟶ lupenone-I ⟶ δ-amyrenone [7,9] could not be excluded.


(VIII)


(IX)


(X)

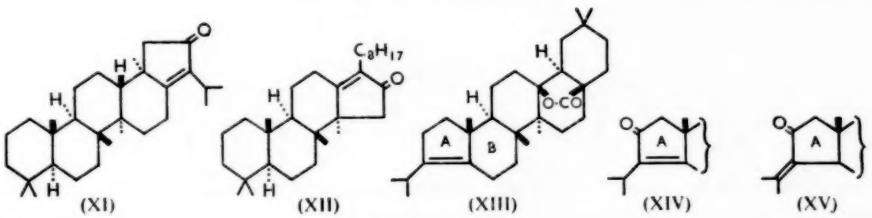
Treatment of hopenone-I with osmium tetroxide followed by reduction with lithium aluminium hydride gave as the main product a triol (X; R = H). This formed only a monoacetate, consistent with the presence of two tertiary hydroxyl groups derived from a tetrasubstituted double bond in hopenone-I. Treatment of the triol monoacetate with lead tetra-acetate gave a diketone having a strong infrared band at 1708 cm.$^{-1}$ due to two carbonyl groups and a medium band at 1403 cm.$^{-1}$ indicative of the methylene of a $-CH_2{\cdot}CO-$ group. These data are consistent with structure (VIII) for hopenone-I.

Oxidation of hopene-I with sodium dichromate in acetic acid–benzene gave as main components an αβ-unsaturated ketone (XI), $C_{30}H_{48}O$, and a saturated ketone, the structure of which is discussed later. The αβ-unsaturated ketone was shown spectroscopically to be a *cyclo*pentenone with a tetrasubstituted double bond. It had bands at 1697 (C=O), 1636 (C=C), and 1409 ($CH_2{\cdot}CO$) cm.$^{-1}$ and its ultraviolet spectrum had a maximum at 2430 Å ($\varepsilon = 13{,}200$). Similar infrared bands are found with other *cyclo*pentenones, notably 16-oxo*iso*euphenyl acetate (XII) with bands at 1692 and 1637 cm.$^{-1}$.[10,11] The ultraviolet spectrum of compound (XII) ($\lambda_{max.}$ 2430 Å; $\varepsilon = 12{,}600$) is also similar, showing, as in the case of the product from hopene-I, the hypsochromic shift of *ca.* 100 Å characteristic of *cyclo*pentenones. This evidence is consistent with structure (XI) for the αβ-unsaturated ketone and provides further support for structure (VIII) for hopenone-I. Chromic acid oxidation of " anhydro-oleanolic lactone II " [12] (XIII) with a terminal ring similar to that of hopene-I also gives a product with $\lambda_{max.}$ 2400 Å. This was formulated either as the *cyclo*pentenone (XIV) or as the *iso*propylidene*cyclo*pentanone (XV); [cf.12] the latter can now be excluded.

If structure (VIII) correctly represented hopenone-I then it should be possible to prepare it from γ-onocerin (XVI) [13] by conversion of the latter into the saturated diol followed by a retropinacolic dehydration at one end of the molecule and oxidation of the secondary hydroxyl group at the other. At this stage Professor O. Jeger kindly informed

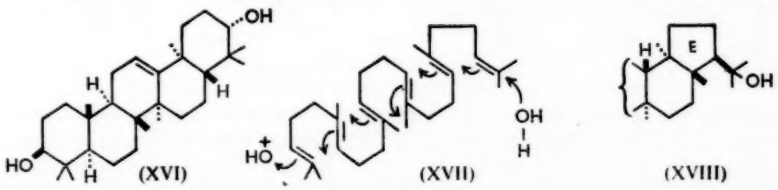
[7] Ames, Halsall, and Jones, *J.*, 1951, 450.
[8] Brownlie, Fayez, Spring, Stevenson, and Strachan, *J.*, 1956, 1377.
[9] Ames, Beton, Bowers, Halsall, and Jones, *J.*, 1954, 1905.
[10] Dawson, Halsall, and Jones, unpublished work.
[11] Arigoni, Viterbo, Dunnenberger, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1954, **37**, 2306.
[12] Ruzicka, Rudowski, Norymberski, and Jeger, *ibid.*, 1946, **29**, 210.
[13] Barton and Overton, *J.*, 1955, 2639.

us that he was investigating the chemistry of γ-onocerin and believed that γ-onocerin could be converted into structure (VIII). He and his colleagues [3] accomplished this and the identities of the products from hydroxyhopanone and γ-onocerin were fully established by determinations of mixed melting point and comparison of infrared spectra. This



(XI) (XII) (XIII) (XIV) (XV)

relation establishes the absolute configuration of seven of the nine asymmetric centres [13,14] in hydroxyhopanone as in (I) and is consistent with its biogenesis from squalene (XVII)



(XVI) (XVII) (XVIII)

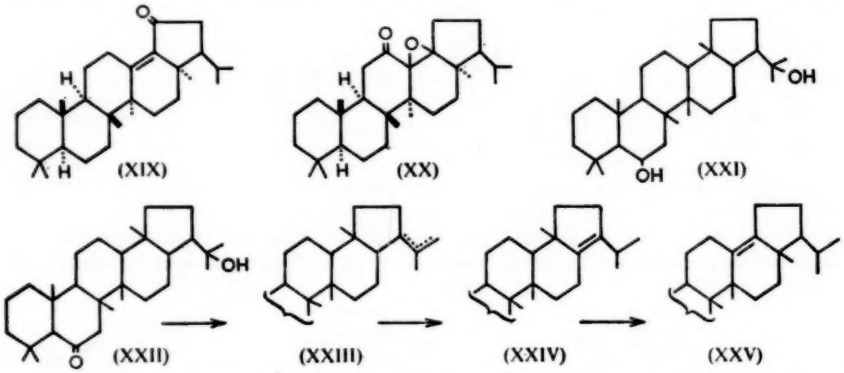
followed by subsequent oxidation of the $C_{(3)}$ hydroxyl group. A completely concerted cyclisation process [15,16] being assumed, the stereochemistry of the two remaining asymmetric centres should be as in (XVIII). [*Added, March 25th*, 1959.—Evidence has now been obtained which confirms the *trans*-fusion of rings D and E (Baddeley, Halsall, and Jones, to be published).]

The structure (IX) given to hopenone-II was based on analogies with the conversion of quinovic acid into novic acid [17] and similar rearrangements.[18,19] The nature of the two carbonyl compounds produced by oxidation of hopene-II with sodium dichromate in acetic acid provided support for this structure. The less polar, $C_{30}H_{48}O$, obtained in 40% yield, had maximal ultraviolet absorption at 2610 Å (ε, 13,900), indicative of a fully-substituted αβ-unsaturated ketone with the double bond exocyclic to two rings [cf. 4 : 4-dimethyl-15-oxocholest-8(14)-en-3β-ol: $\lambda_{max.}$ 2610 Å, ε = 14,700 [20]]. Its infrared spectrum had bands at 1697 and 1615 cm.$^{-1}$, the latter being only slightly the less intense. The band at 1697 cm.$^{-1}$ indicates a keto-group in a five-membered ring, and the high intensity of the 1615 cm.$^{-1}$ band that the αβ-unsaturated ketone is cisoid.[21,22] These data are appropriate to structure (XIX) derived from structure (IX) for hopenone-II. The more polar oxidation product (20%), $C_{30}H_{48}O_2$, gave no colour with tetranitromethane and showed no selective light absorption between 2200 Å and 2600 Å. Its infrared band at 1706 cm.$^{-1}$ was characteristic of a *cyclo*hexanone. These facts, together with the presence of weak infrared bands at 910, 890, 870, and 820 cm.$^{-1}$, probably due to an epoxide,[23]

[14] Schaffner, Viterbo, Arigoni, and Jeger, *J.*, 1956, **39**, 174.
[15] Ruzicka, "Perspectives in Organic Chemistry," Interscience, London, 1956, p. 265.
[16] Eschenmoser, Ruzicka, Jeger, and Arigoni, *ibid.*, 1955, **38**, 1890.
[17] Barton and de Mayo, *J.*, 1953, 3371.
[18] Allan, Spring, Stevenson, and Strachan, *J.*, 1955, 3371.
[19] Allan, Fayez, Spring, and Stevenson, *J.*, 1956, 457.
[20] Woodward, Patchett, Barton, Ives, and Kelly, *J. Amer. Chem. Soc.*, 1954, **76**, 2852.
[21] Cf. Eschenmoser, Schinz, Fischer, and Colonge, *Helv. Chim. Acta*, 1951, **34**, 2329.
[22] Cf. Heusser, Saucy, Anliker, and Jeger, *ibid.*, 1952, **35**, 2090.
[23] Cf. Sallmann and Tamm, *ibid.*, 1956, **39**, 1340; Bible, Placek, and Muir, *J. Org. Chem.*, 1957, **22**, 607; Meda, Camerino, Alberti, and Vercellone, *Gazzetta*, 1955, **85**, 41.

justify the formulation of this compound as the oxo-epoxide (XX), a typical product of oxidation by chromic acid.

Very recently the structure (XXI) with the same gross carbon skeleton as hydroxyhopanone has been suggested [6] for zeorin.[24] Both hydroxyhopanone (I) and zeorinone (XXII) give a similar series of products on acid isomerisation, *iso*zeorininone (XXIII) [6]



corresponding to hopenone (IV and V), zeorininone (XXIV) [6] to hopenone-I (VIII), and *neo*zeorininone (XXV) [6] to hopenone-II (IX). Oxidation of zeorininone and *neo*zeorininone gives compounds [6] analogous to those, *i.e.*, (X), (XIX), and (XX), formed from hopenone-I and hopene-II. The molecular rotation changes for the sequence zeorinone (XXII) to *neo*zeorininone (XXV) and from hydroxyhopanone to hopenone-II are given in Table 2. In Table 3 the rotations of the products of oxidation of hopene-I and hopene-II are compared with the corresponding products from zeorininone and *neo*zeorininone. Apart from the differences between zeorinone and zeorininone and between hydroxyhopane and hopenone-I, the changes are of the same sign and size, suggesting that the stereochemistry at $C_{(13)}$, $C_{(14)}$, and $C_{(18)}$ is the same in both zeorin and hydroxyhopane. The observed differences would be compatible with variations at the two centres in ring E, $C_{(17)}$ and $C_{(21)}$, and hydroxyhopanone and zeorin may differ at one or both of these centres.

TABLE 2.

	$[M]_D$	$\Delta[M]_D$		$[M]_D$	$\Delta[M]_D$
Zeorinone	+154° [a]	−23°	Hydroxyhopanone (I)	+305° [b]	−21°
*iso*Zeorininone (XXIII)	+131° [a]	−42	Hopenone (IV and V)	+284° [b]	+38
Zeorininone (XXIV)	+89° [a]	−97	Hopenone-I (VIII)	+322° [c]	−89
*neo*Zeorininone (XXV)	−8° [a]		Hopenone-II (IX)	+233° [d]	

[a] Ref. 24. [b] Ref. 1. [c] This is calculated from the value given for hopenone-I from γ-onocerin; cf. ref. 3. [d] This paper.

TABLE 3.

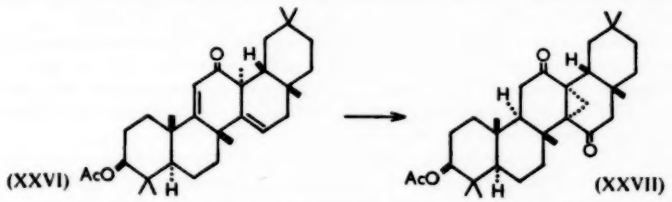
	$[M]_D$	$\Delta[M]_D$		$[M]_D$	$\Delta[M]_D$
Epoxy-ketone (XX) [a] from hopene-II	+462°	+454°	Epoxy-dione from [b] *neo*zeorinone	+413°	+421°
Hopene-II [a]	+8		*neo*Zeorininone [c]	−8	
αβ-Unsaturated ketone [a] (XIX) from hopene II	+197	+189	αβ-Unsaturated ketone [b] from *neo*zeorininone	+171	+179
Triol monoacetate [a] (X; R = Ac) from hopenone-I	+113	−145	Triol monoacetate from [b] zeorinin acetate	+266	−106
Diketone fission [a] product	−32		Diketone fission [b] product	−160	

[a] This paper. [b] Ref. 6. [c] Ref. 24.

As indicated above, one of the oxidation products from hopene-I is a saturated ketone, $C_{30}H_{48}O$, with its keto-group in a five-membered ring (indicated by a band at 1742 cm.$^{-1}$

[24] Barton and Bruun, *J.*, 1952, 1683.

of moderate intensity). It gave no colour with tetranitromethane and showed negligible absorption between 1900 and 2600 Å. This indicates the absence of a double bond and that the ketone must be hexacyclic, a new *cyclo*alkane ring having been formed during the



oxidation. It is likely that this is a *cyclo*propane ring, although no band at *ca.* 3040 cm.$^{-1}$, indicating a methylene group in such an environment,[25] was present. An example of the formation of a *cyclo*alkane ring during oxidation with chromic acid is found in the conversion of 12-oxo*iso*oleana-9(11) : 14-dien-3β-yl acetate (XXVI) by vigorous oxidation with chromic acid into a product which is probably 12 : 14-dioxo-13 : 27-*cyclo*olean-9(11)-en-3β-yl acetate (XXVII).[26,27]

Experimental

M. p.s are uncorrected. Rotations were determined for chloroform solutions at room temperature. Ultraviolet spectra were obtained on a Cary recording spectrophotometer. Measurements of end absorption were observed at maximum sensitivity in 2-mm. cells at optical densities in the range 0·3 to 0·5. Infrared spectra were determined for carbon disulphide solutions unless otherwise stated. The alumina used for chromatography was Peter Spence Grade " H " and, unless otherwise stated, was deactivated with 5% of 10% aqueous acetic acid. Light petroleum refers to the fraction with b. p. 60—80°.

Treatment of Hydroxyhopanone with 6% (v/v) Sulphuric Acid in Acetic Acid.—The ketol (1·06 g.) in acetic acid (110 c.c.) was treated, with cooling, with concentrated sulphuric acid (7·2 c.c.) in acetic acid (10 c.c.). A precipitate formed immediately. After 24 hr. at 20° this was filtered off, washed with methanol, and dried (675 mg.). Crystallisation from acetone–chloroform (3 : 1) gave hopenone-I [3-oxohop-17(21)-ene; (VIII)] as needles, m. p. 197—197·5°, $[\alpha]_D$ +93° (*c* 0·74). {Schaffner *et al.*[3] report that the rotation of this sample as determined by them is +76° (*c* 0·35). For hopenone-I from γ-onocerin they report $[\alpha]_D$ +77°} (Found: C, 84·8; H, 11·4. Calc. for $C_{30}H_{48}O$: C, 84·85; H, 11·4%). Light absorption: ε at 2100 Å = 6250; at 2150 Å = 3480; at 2200 Å = 1700; infrared bands at 1706s and 830—800w (br.) cm.$^{-1}$. Hopenone-I gave a yellow colour with tetranitromethane.

The filtrate was diluted with water. Ether extraction gave a pale yellow solid (315 mg.) chromatography and fractional crystallisation of which showed that it was a mixture of hopenone-I and lower-melting material (see hopenone-II below).

Isomerisation of Hopenone-I (VIII) *with 15% Sulphuric Acid in Acetic Acid.*—Hopenone-I (370 mg.) in acetic acid (65 c.c.) and benzene (25 c.c.) was treated with concentrated sulphuric acid (12·75 c.c.) in acetic acid (20 c.c.). After the mixture had been kept for 18 hr. at 20° (no precipitate) it was worked up in the usual manner to give a yellow gum (350 mg.) which was adsorbed from light petroleum (20 c.c.) on alumina (20 g.). Elution with light petroleum (20 c.c.) gave a gum (51 mg.), obtained as plates, m. p. 165—175° after softening above 140°, from methanol. Further elution with light petroleum (80 c.c.) gave a solid (222 mg.), obtained as needles (from methanol), m. p. 145—150°. Finally elution with light petroleum (100 c.c.) gave a solid (46 mg.), obtained as needles and plates (from methanol), m. p. 140—152°. Further crystallisation of the middle fraction from methanol gave *hopenone-II* (IX) as needles, m. p. 152—154°, $[\alpha]_D$ +55° (*c* 1·06) (Found: C, 84·6; H, 11·7. $C_{30}H_{48}O$ requires C, 84·85; H, 11·4%).

*Isomerisation of Hopenone.**—Hopenone (0·69 g.) was dissolved in acetic acid (55 c.c.), and

* This is the product of dehydration of hydroxyhopanone with phosphoryl chloride and is a mixture of the *iso*propylidene (hopenone-a) and *iso*propenyl (hopenone-b) isomers.

[25] Cole, *J.*, 1954, 3807.
[26] Beaton, Easton, Macarthur, Spring, and Stevenson, *J.*, 1955, 3992.
[27] Johnson and Spring, *J.*, 1954, 1556.

XUM

a mixture of acetic acid (10 c.c.) and concentrated sulphuric acid (5·5 c.c.) added. Crystals began to separate after a few minutes. After 24 hr. the solid was filtered off and crystallised from acetone–chloroform to give hopenone-I, m. p. 197—199°. Addition of water to the acidic filtrate precipitated a solid from which more hopenone-I and some hopenone-II were obtained.

Hopene-I.—Hopenone-I (223 mg.) was reduced by the Huang-Minlon procedure, diethylene glycol (60 c.c.), hydrazine hydrate (3 c.c.; 100%), and then potassium hydroxide (2·15 g.) being used. Isolation with ether afforded a solid (215 mg.) which crystallised from acetone to give *hopene-I* [hop-17(21)-ene] as needles, m. p. 178—180°, $[\alpha]_D$ +49·5° (*c* 0·98) (Found: C, 87·65; H, 12·1. $C_{30}H_{50}$ requires C, 87·75; H, 12·25%).

Hopene-II.—Hopenone-II (680 mg.) was reduced by the Huang-Minlon procedure, diethylene glycol (100 c.c.), hydrazine hydrate (4 c.c.; 100%), and then potassium hydroxide (3·3 g.) being used. Isolation in the usual manner and crystallisation of the product (620 mg.) from acetone gave *hopene-II* as plates (380 mg.), m. p. 194—196° undepressed on admixture with a sample obtained by acid isomerisation of hopene-ab (see below), $[\alpha]_D$ +2° (*c* 1·38) (Found: C, 87·5; H, 12·45. $C_{30}H_{50}$ requires C, 87·75; H, 12·25%). The mother liquor afforded plates (127 mg.), m. p. 155—157°, $[\alpha]_D$ +29·5° (*c* 0·79), the infrared spectrum of which was almost identical with that of hopene-II.

Isomerisation of Hopene with Sulphuric Acid in Acetic Acid.—Hopene (1·09 g.) was dissolved in acetic acid (220 c.c.) and benzene (70 c.c.) at 100°. Evaporation under reduced pressure removed most of the benzene. Sulphuric acid (12 c.c.) was added at 60°. After 7 hr. at 20° the precipitate (915 mg.), m. p. mainly 162—164° (solid remaining up to 174°), was isolated. Crystallisation from methanol–acetone gave two similar fractions; rotation and infrared data indicate that they are a mixture of hopene-I (*ca.* 80%) and hopene-II (*ca.* 20%).

The two fractions (667 mg.) were treated in benzene (75 c.c.) with acetic acid (255 c.c.) and concentrated sulphuric acid (45 c.c.) at 20°. After 18 hr. the precipitate was collected (437 mg.; m. p. 192—196°). The filtrate afforded a brown semi-solid (230 mg.) not yet examined. Crystallisation of the precipitate from acetone gave hopene-II as plates (395 mg.), m. p. and mixed m. p. 195—196·5°, $[\alpha]_D$ +1·5°.

γ-Lupene.—This was prepared as described by Heilbron, Kennedy, and Spring [4] but with a contact time of 9 min. γ-Lupene formed hard needles (from ethyl acetate), m. p. 193—197°, $[\alpha]_D$ −18° (*c* 1·05) (lit. value [3]: m. p. 197—199°, $[\alpha]_D$ −19·7°).

iso-*γ-Lupene.*—This was prepared by refluxing γ-lupene in acetic acid for 12 hr.[4] It formed leaflets (from acetone–methanol), m. p. 128—130°, $[\alpha]_D$ +12° (*c* 1·3) (lit. value [5]: m. p. 133—134° [evacd. capillary], $[\alpha]_D$ +14°).

δ-Amyrenone.—This was prepared by acid isomerisation of β-amyrenone; [7] it had m. p. 201—203°, $[\alpha]_D$ −10° (*c* 1·5) (lit. value: m. p. 200—202·5°, $[\alpha]_D$ −12°).

Hydroxylation of Hopenone-I (VIII).—Hopenone-I (940 mg.) in dioxan (10 c.c.) and pyridine (25 c.c.) was treated with osmium tetroxide (650 mg.; 1·23 mol.) at 20°; a black precipitate formed rapidly. After 67 hr. the solution was evaporated, tetrahydrofuran (20 c.c.) and lithium aluminium hydride (1 g.) were added, and the solution was refluxed for 2 hr. The product (1 g.), isolated with ether, was crystallised from acetone–methanol to give 3β : 17ξ : 21ξ-*trihydroxyhopane* (X; R = H) as laths (660 mg.), m. p. 244—246°, $[\alpha]_D$ +16·5° (*c* 1·2) (in pyridine) (Found: C, 76·4; H, 11·55. $C_{30}H_{52}O_3$,MeOH requires C, 76·55; H, 11·45%). It gave no colour with tetranitromethane. The mother liquor from the first crystallisation was evaporated, and the residue filtered in benzene–ether (1 : 1) through alumina. The product (255 mg.) formed needles (from methanol), m. p. 207—211°, $[\alpha]_D$ +22·5° (*c* 1·17) (in pyridine). The infrared spectrum was almost identical with that of the main product. The needles gave no colour with tetranitromethane. It is probably isomeric with the above triol, with the glycol grouping in the opposite and more hindered *cis* configuration.

The triol (580 mg.) in pyridine (7 c.c.) was treated with acetic anhydride (3 c.c.) for 9 hr. at 20°. Dilution with water gave a solid which was chromatographed on alumina to give *hopane*-3β : 17ξ : 21ξ-*triol* 3-*monoacetate* (X; R = Ac) (580 mg.) as needles (from acetone–methanol), m. p. 273—278° (after transition above 220°), $[\alpha]_D$ +22·5° (*c* 1·44) (Found: C, 76·25; H, 11·0. $C_{32}H_{54}O_4$ requires C, 76·45; H, 10·85).

Fission of the Triol 3-*Monoacetate* (X; R = Ac) *with Lead Tetra-acetate.*—The triol 3-monoacetate (68 mg.) in benzene (6 c.c.) and acetic acid (4 c.c.) was treated with a solution of lead tetra-acetate in acetic acid (1·48%; 5 c.c. = 1·23 mol.), and benzene (5 c.c.) was added. 1 mol.

of the oxidant was consumed in less than 20 min. at 20°. The mixture was then poured into water containing potassium iodide and sodium thiosulphate. Isolation in the usual manner afforded a 3β-*acetoxy*-17 : 21-*dioxo*-E-seco*hopane*, which crystallised from methanol as needles, m. p. 195—196°, $[\alpha]_D$ −6·5° (*c* 0·38) (Found: C, 77·15; H, 10·5. $C_{32}H_{52}O_4$ requires C, 76·75; H, 10·45%). $\nu_{max.}$ 1732s (OAc), 1708vs (br.) (2 C=O groups), 1403m (−CH_2·CO−) cm.$^{-1}$.

The diketo-acetate (47 mg.) in methanol (5 c.c.) was treated with potassium hydroxide (525 mg.) in methanol (4 c.c.) at 20° for 7 hr. and then at 90° for 2 min. Isolation in the usual manner gave the diketo-alcohol as a gum (40 mg.; insufficient for further purification); $\nu_{max.}$ 3600—3350 (br.) and 1030 (OH), 1708s (C=O), 1698ms (inflex.) (C=O) cm.$^{-1}$.

Hydroxylation of Hopene-I.—Hopene-I (145 mg.) in ether (10 c.c.) and pyridine (3 c.c.) was treated with osmium tetroxide (134 mg.) at 20° for 24 hr. The mixture was evaporated at 100°/0·2 mm. and the residual osmate heated under reflux with lithium aluminium hydride (600 mg.) in tetrahydrofuran (20 c.c.) for 1 hr. Isolation in the usual manner afforded a solid (155 mg.) which was adsorbed on alumina (9 g.) from light petroleum–benzene (7 : 3; 10 c.c.). Elution with this solvent (20 c.c.) gave a gummy solid (29 mg.). Further elution with the same solvent (60 c.c.) gave *hopane*-17ξ : 21ξ-*diol* (115 mg.) as plates (from methanol–acetone), m. p. 225—226°, $[\alpha]_D$ +12·5° (*c* 1·44) (Found: C, 80·8; H, 11·9. $C_{30}H_{52}O_2$ requires C, 81·0; H, 11·8%).

Oxidation of Hopene-I with Sodium Dichromate.—To hopene-I (785 mg.) in acetic acid (50 c.c.) and benzene (20 c.c.) at 50° was added sodium dichromate (2·33 g.; 12·3 mol.) in acetic acid (15 c.c.). The temperature was raised gradually during 45 min. to 83° and the solution kept at this temperature for a further 45 min. Ethanol (10 c.c.) and water were then added. Isolation with ether gave a neutral pale yellow solid (790 mg.) ($\lambda_{max.}$ 2430 Å, ε *ca.* 8000). This was adsorbed from light petroleum–benzene (9 : 1; 35 c.c.) on alumina (50 g.). This solvent (100 c.c.) eluted a solid (294 mg.) which gave a saturated *ketone* as plates (123 mg.) (from acetone–methanol), m. p. 271—273° (after change to needles above 200°), $[\alpha]_D$ +44·5° (*c* 0·92) (Found: C, 84·65; H, 11·65. $C_{30}H_{48}O$ requires C, 84·85; H, 11·35%). $\nu_{max.}$ (in Nujol): 1742ms and 1411 cm.$^{-1}$ (C=O and CH_2·CO of *cyclo*pentanone). Light absorption between 1900 and 2600 Å was negligible. It gave no colour with tetranitromethane. The mother-liquor from the first crystallisation above afforded impure αβ-unsaturated ketone (see below).

Further elution with light petroleum–benzene (9 : 1 and 8 : 2; 400 c.c.) yielded a solid (468 mg.) which gave the αβ-unsaturated ketone (XI) as needles (320 mg.) (from methanol), m. p. 172—173·5°, $[\alpha]_D$ +4° (*c* 1·0) (Found: C, 85·0; H, 11·45. $C_{30}H_{48}O$ requires C, 84·85; H, 11·4%). $\nu_{max.}$ (in Nujol): 1697vs and 1636s (C=O and C=C of *cyclo*pentenone), 1407ms (CH_2·CO) cm.$^{-1}$; $\lambda_{max.}$ 2430 Å (ε 13,200). A very pale yellow colour was given with tetranitromethane.

Oxidation of Hopene-II with Sodium Dichromate.—To hopene-II (675 mg.) in acetic acid (40 c.c.) and benzene (30 c.c.) at 50° was added sodium dichromate (2·0 g.; 12·3 mol.) in acetic acid. The method of the preceding oxidation was then employed. Isolation gave a neutral pale yellow solid (690 mg.) ($\lambda_{max.}$ 2160 Å; ε *ca.* 7300) which was adsorbed from light petroleum–benzene (10 : 1; 33 c.c.) on alumina (45 g.).

Elution with light petroleum–benzene (9 : 1; 250 c.c.) produced a solid (283 mg.) which gave the αβ-*unsaturated ketone* (XIX) as plates (from methanol), m. p. 253—254·5°, $[\alpha]_D$ +46·5° (*c* 1·0) (Found: C, 84·7; H, 11·45. $C_{30}H_{48}O$ requires C, 84·85; H, 11·4%). $\nu_{max.}$ (in Nujol): 1697s (*cyclo*pentenone), 1615s (slightly lower) (C=C), (1409) (CH_2·CO) cm.$^{-1}$. It gave a pale yellow colour with tetranitromethane.

Elution with light petroleum–benzene (1 : 1; 350 c.c.) gave several fractions (300 mg.) which on crystallisation from methanol–acetone gave the *keto-epoxide* (XX) (122 mg.) as plates, m. p. 240—243°, $[\alpha]_D$ +105° (*c* 0·97) (Found: C, 81·85; H, 10·7. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%). $\nu_{max.}$ (in Nujol): 1706s (six-membered ring C=O) 910, 890, 870, 820 (epoxide?) cm.$^{-1}$. There was negligible light absorption between 2000 and 2600 Å. It gave no colour with tetranitromethane.

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374. *Fluorination of* 1 : 2 : 3 : 4-*Tetrachlorobutadiene with Chlorine Fluorides.*

By J. Muray.

Tetrachlorohexafluoro-, pentachloropentafluoro-, and hexachlorotetrafluoro-butanes have been prepared by the reaction of 1 : 2 : 3 : 4-tetrachlorobutadiene with chlorine fluorides. The yields of the individual chlorofluorobutanes depended on the conditions and the fluorinating agent used. Dechlorination of the butanes by zinc gave the appropriate perfluoro- and chlorofluoro-butadienes.

Very little work has been done on the fluorination of organic compounds with chlorine fluorides. Ellis and Musgrave [1] reported the fluorination of aromatic hydrocarbons to products with low halogen contents and there are patents covering the preparation of chlorofluorocarbon oils.[2]

This paper describes work on the preparation of chlorofluorobutanes and the evaluation of chlorine mono- and tri-fluoride as fluorinating agents for organic compounds. The work involved liquid-phase reactions of 1 : 2 : 3 : 4-tetrachlorobutadiene with chlorine mono- and tri-fluoride under conditions which ensure dissipation of the energy released in the highly exothermic reactions. This requirement was satisfied by using a relatively large charge in a nickel vessel in which the chlorine fluoride feed-line was placed ¼ in. below the centre of a high speed vaned-disc stirrer, the arrangement providing good dispersion of the reagent throughout the whole charge. The fluorinating agent was diluted with nitrogen in the early stages of the reaction.

For determination of their structures the products were dechlorinated to dienes which in turn were brominated and/or chlorinated by established methods.

Experimental

1 : 2 : 3 : 4-Tetrachlorobutadiene was separated from the by-products obtained in manufacture of trichloroethylene. It was purified by fractional distillation through a still with an efficiency of 15 theoretical plates. The tetrachlorobutane used in the fluorinations was a mixture of the liquid and the solid stereoisomer, identified by their physical properties.[3] The solid isomer was separated by cooling the mixture and filtering it off at −20°. It was purified by recrystallisation from ethyl alcohol.

The liquid isomer had b. p. 188°, n_D^{20} 1·557 (Found: C, 24·1; H, 1·1; Cl, 75·1%; *M*, 193. Calc. for $C_4H_2Cl_4$: C, 25; H, 1·05; Cl, 73·95%; *M*, 192). The solid isomer had b. p. 189°, m. p. 49·5° (Found: C, 24·2; H, 1·0; Cl, 75·2%; *M*, 197).

Reaction of 1 : 2 : 3 : 4-*Tetrachlorobutadiene with Chlorine Trifluoride.*—The reaction was carried out in a 4 l. nickel vessel under a water-cooled condenser. Gaseous chlorine trifluoride, initially diluted with 5 volumes of nitrogen, was passed through vigorously stirred tetrachlorobutadiene (3800 g.), the temperature of which was gradually raised from 20° to 150°. The flow-rate of chlorine trifluoride was gradually increased from 10 to 40 l./hr., and dilution by nitrogen was reduced to 1 : 1 during 10 hr.; nitrogen was cut off completely after 20 hr.

The reaction was stopped when the refractive index of the charge remained practically constant at n_D^{20} 1·449 ± 0·001, a total of 3800 g. of chlorine trifluoride having been passed. During the run samples of the charge were withdrawn and analysed.

Fractional distillation of the final product (6030 g.) showed that it consisted of: (i) 1 : 2 : 3 : 4-tetrachloro-1 : 1 : 2 : 3 : 4 : 4-hexafluorobutane (3%), n_D^{20} 1·385, b. p. 135° (Found: C, 15·6; Cl, 47·8; F, 36·1. Calc. for $C_4Cl_4F_6$: C, 15·8; Cl, 46·7; F, 37·5%) (Miller [4] gives b. p. 134·5°, n_D^{20} 1·385); (ii) a product $C_4Cl_5F_5$ (20%), n_D^{20} 1·423, b. p. 172° (Found: C, 15·0; Cl, 56·9;

[1] Ellis and Musgrave, *J.*, 1950, 3608; 1953, 1063.
[2] B.P. 633,678, 676,374, 695,811, 738,289, 774,737; Canad. P. 556,636.
[3] Huntress, "The Preparation, Properties, Chemical Behaviour, and Identification of Organic Compounds," J. Wiley and Sons, Inc., New York, 1948.
[4] Miller, Nat. Nuclear Energy Series Div. VII, Vol. I, "Preparation, Properties and Technology of Fluorine and Organic Fluorine Compounds," 1951, pp. 567—685.

F, 28·2. Calc. for $C_4Cl_5F_5$: C, 15·0; Cl, 55·4; F, 29·6%) (Miller [4] gives b. p. 104·5°/100 mm., n_D^{20} 1·420); (iii) 1 : 1 : 2 : 3 : 4 : 4-hexachloro-1 : 2 : 3 : 4-tetrafluorobutane (50%), n_D^{20} 1·455, b. p. 209° (Found: C, 14·2; Cl, 63·5; F, 22·2. Calc. for $C_4Cl_6F_4$: C, 14·2; Cl, 63·2; F, 22·6%) (Miller [4] gives b. p. 134°/100 mm., n_D^{20} 1·457); and (iv) material, $C_4Cl_7F_3$, n_D^{20} 1·488, b. p. 245°/760 mm., 92°/20 mm. (Found: C, 13·7; Cl, 70·3; F, 16·2. Calc. for $C_4Cl_7F_3$: C, 13·6; Cl, 70·3; F, 16·1%) (Miller [4] gives b. p. 125°/25 mm., n_D^{20} 1·491). The rest of the product was in intermediate fractions.

Reaction of 1 : 2 : 3 : 4-*Tetrachlorobutadiene with Chlorine Monofluoride.*—The reaction was carried out in a vessel similar to that recorded above but of 1 l. capacity. Chlorine monofluoride was prepared by reaction of chlorine trifluoride with chlorine at 360° and was used directly. The gas, initially diluted with 3 volumes of nitrogen, was passed through tetrachlorobutadiene (382 g.) at the rate of 18 l./hr. at 20° increasing gradually to 120°. The flow of nitrogen was gradually decreased so that the fluorinating agent was undiluted after 15 hr. The reaction was stopped when the refractive index remained practically constant at 1·418. Samples were withdrawn during the reaction and analysed.

Fractional distillation of the final product (428 g.) gave 15% of the tetrachlorohexafluorobutane, b. p. 135°, n_D^{20} 1·385, 50% of the pentachloropentafluorobutane, b. p. 172°, n_D^{20} 1·423, and about 25% of a mixture of hexachlorotetrafluorobutane and hydrogen-containing chlorofluorobutanes.

Reaction of Chlorofluorobutanes with Chlorine Monofluoride.—The reaction was carried out in the 1 l. vessel, but the condenser was replaced with a still head so that the product distilled off as it was formed. Undiluted chlorine monofluoride was passed through a mixture of chlorofluorobutanes (n_D^{20} 1·449; 542 g.), at 150—155°, previously obtained in the reaction of 1 : 2 : 3 : 4-tetrachlorobutadiene with chlorine trifluoride. The product (440 g.) consisted of 70% of tetrachlorotetrafluoro- (b. p. 135°, n_D^{20} 1·385) and 10% of pentachloropentafluorobutane (b. p. 172°, n_D^{20} 1·423), the rest being chlorofluorocarbons of less than 4 carbon atoms and $C_4Cl_6F_4$.

Dechlorination of 1 : 2 : 3 : 4-*Tetrachloro*-1 : 1 : 2 : 3 : 4 : 4-*hexafluorobutane.*—The chlorofluorobutane was added dropwise to the stirred mixture of zinc dust (about 400 g.), butyl alcohol (1·2 l.), and acetic acid (5 ml.) at 85—95°; in no run were more than 2 g. of the chlorofluorobutane used per g. of zinc dust. The product passed through a fractionating column kept at 10° and was collected in traps at 0° and −80°.

The product was refluxed for 3 hr. over phosphoric oxide and fractionally distilled in a low-temperature still with an efficiency of 20 theoretical plates. Practically all the product boiled at 5·5° and had a molecular weight of 159·5 ± 0·5 (65% yield). Miller [4] and Haszeldine [5] reported 6° and 5·8° respectively for the b. p. of perfluorobutadiene.

Dechlorination of Pentachloropentafluorobutane.—The dechlorination was carried out as above except that the fractionating column was at room temperature instead of 10°. The product, after refluxing over phosphoric oxide, was distilled first at atmospheric pressure, then at 80 mm. in the low-temperature still. The final product (60% yield) boiled at 38°/760 mm. and −11·5°/80 mm. and had n_D^{20} 1·3385 ± 0·0005 (Found: *M*, 178·5 ± 0·5). Miller [6] prepared $CF_2{:}CCl{\cdot}CF{:}CF_2$, b. p. 37°.

Dechlorination of 1 : 1 : 2 : 3 : 4 : 4-*Hexachloro*-1 : 2 : 3 : 4-*tetrafluorobutane.*—Dechlorination was carried out as above with the fractionating column at 60°. The crude product distilled at 75—80° at atmospheric pressure. The distillate was refluxed over phosphoric oxide, then fractionated at 55 mm.; most of it then boiled at 11° ± 1° and had *M*, 195 ± 1. A fraction of b. p. 12—14°, having *M*, 194 ± 2, was also obtained. It is possible that both fractions were isomers of dichlorotetrafluorobutadiene. The mixed fractions (48% yield) had b. p. 79° ± 1°, n_D^{25} 1·404. Miller [4,6] gives for $CClF{:}CF{\cdot}CF{:}CClF$ b. p. 78°, n_D^{20} 1·402, and for $CF_2{:}CCl{\cdot}CCl{:}CF_2$ b. p. 69—70°, n_D^{20} 1·3832. Haszeldine and Osborne [7] give for $CCl{:}CF{\cdot}CF{:}CClF$ b. p. 79°, n_D^{20} 1·403.

Derivatives of Perfluoro- and Chlorofluoro-butadienes.—Addition of bromine to perfluorobutadiene was carried out at 0° rising to 105°, and to monochloropentafluoro- and dichlorotetrafluorobutadiene at 20—150°. In each case the product consisted of a single fraction of constant b. p. and *n*. Addition of chlorine to dibromohexafluorobutene obtained in the addition of bromine to perfluorobutadiene occurred only at 120° in light of 5300—4500 Å.

[5] Haszeldine, *J.*, 1952, 4423.
[6] Miller, U.S.P. 2,668,182.

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The products were: Dibromohexafluorobutene, b. p. 102°, n_D^{20} 1·396 (Found: C, 14·6; Br, 50·1; F, 35·1. Calc. for $C_4Br_2F_6$: C, 14·9; Br, 49·7; F, 35·4%) (Haszeldine [5] gives b. p. 99—100°, n_D^{20} 1·394). Dibromodichlorohexafluorobutane (from $C_4Br_2F_6$) (Found: C, 12·5; Br, 42·2; Cl, 19; F, 25·8%; *M*, 394 ± 1. Calc. for $C_4Cl_2Br_2F_6$: C, 12·2; Br, 40·7; Cl, 18·1; F, 29·0%; *M*, 393). Dibromochlorotrifluorobutane (from C_4ClF_5), b. p. 137°, n_D^{20} 1·4325 (Found: C, 14·3; Br, 47·0; Cl, 10·9; F, 27·9. Calc. for $C_4ClBr_2F_5$: C, 14·2; Br, 47·3; Cl, 10·5; F, 28·0%). Dibromodichlorotetrafluorobutane (from $C_4Cl_2F_4$), b. p. 80°/10 mm., n_D^{20} 1·477 (Found: C, 13·7; Br, 43·6; Cl, 21·2; F, 20·6. Calc. for $C_4Cl_2Br_2F_4$: C, 13·5; Br, 45·1; Cl, 20·0; F, 21·4%). Miller [4] and Haszeldine [5] obtained $C_4Br_4F_6$ in the bromination of perfluorobutadiene at 120° in ultraviolet light (*i.e.*, under more vigorous conditions).

Discussion

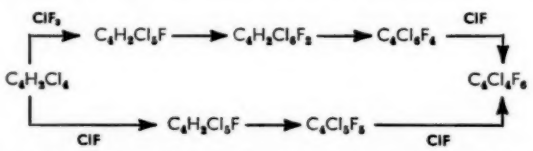
The results show that the yields of the individual chlorofluorobutanes, $C_4Cl_4F_6$, $C_4Cl_5F_5$, $C_4Cl_6F_4$, and $C_4Cl_7F_3$, depend on the reaction conditions, the fluorinating agent, and the extent to which the reactions are carried out (as indicated by the refractive index).

The hexachlorotetrafluorobutane is best prepared by reaction of tetrachlorobutadiene with chlorine trifluoride carried out to n 1·448 ± 0·001. Good yields of the pentachloropentafluoro-compound are obtained by reaction of the hexachlorotetrafluorobutane with chlorine monofluoride until n drops to 1·418 ± 0·003. More than 80% of hexachlorotetrafluoro- and/or pentachloropentafluoro-butane is converted into the tetrachlorohexafluorobutane by chlorine monofluoride at 150° if the product, boiling at 135°, is distilled off as it is made.

Only perfluorobutadiene was obtained on dechlorination of the tetrachlorohexafluoro-product; this butadiene, with bromine and then chlorine gave a quantitative yield of dibromodichlorohexafluorobutane; so the chlorofluorobutane must have been $CClF_2{\cdot}CClF{\cdot}CClF{\cdot}CClF_2$ and the product of dechlorination perfluorobutadiene.

Structures of the products $C_4Cl_5F_5$ and $C_4Cl_6F_4$ cannot be assigned with certainty but the exclusive formation of C_4ClF_5 and $C_4Cl_2F_4$ in their dechlorination indicates that at least one chlorine atom must have been attached to each carbon atom present. Agreement between the boiling points and refractive index of the butadiene derived from $C_4Cl_6F_4$ with that reported [4,7] for $CClF{:}CF{\cdot}CF{:}CClF$ suggests the structure of $CCl_2F{\cdot}CClF{\cdot}CClF{\cdot}CCl_2F$ although $CClF_2{\cdot}CCl_2{\cdot}CClF{\cdot}CCl_2F$ and $CClF_2{\cdot}CClF{\cdot}CCl_2{\cdot}CCl_2F$ are not excluded. No reference could be found in the literature to the physical properties of these compounds or to $CF_2{:}CCl{\cdot}CF{:}CClF$ and $CF_2{:}CF{\cdot}CCl{:}CClF$, which can be derived from them by dechlorination.

The compositions of samples taken during the fluorinations indicate the annexed reactions.



Since similar observations were made for the reactions of hexachlorobutadiene, chlorinated ethylenes, and chlorinated aromatic compounds with the chlorine fluorides, the following generalisations can be made: (*a*) Chlorine trifluoride is more vigorous and efficient than the monofluoride in chlorofluorination of unsaturated chlorinated hydrocarbons. It is particularly useful for saturation of double bonds and replacement of hydrogen by halogen. (*b*) Chlorine monofluoride is a useful reagent for replacement of chlorine by fluorine in chlorofluorocarbons containing more chlorine than fluorine. It does not saturate double bonds or replace hydrogen by halogen as readily as does chlorine trifluoride.

The more vigorous nature of the reactions with chlorine trifluoride than of those with

[7] Haszeldine and Osborne, *J.*, 1955, 3880.

chlorine monofluoride probably results from easier initiation of the reaction, thought to involve a radical mechanism. Chlorine trifluoride can be considered as very similar to fluorine because of the low heat of dissociation,[8] $ClF_3 \rightleftharpoons F_2 + ClF$, $\Delta H = 26{\cdot}5$ kcal./mole. Less energy is required in the dissociation of ClF_3 than in breaking the F–F bond in fluorine or the Cl–F bond in chlorine monofluoride, the respective bond dissociation energies being 36·6 (ref. 9) and 60·3 kcal./mole (ref. 10). The suggestion that the reactions of tetrachlorobutadiene with chlorine fluorides involve free radicals is supported by the results obtained in more recent, unpublished work in which tetrachloroethylene and chlorinated aromatic compounds were treated with a mixture of chlorine trifluoride and oxygen.

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[8] Schäfer and Wicke, *Z. Elektrochem.*, 1948, **25**, 205.
[9] Nat. Bur. Standards, "Selected Values of Chemical Thermodynamic Properties."
[10] Schmitz and Schumacher, *Z. Naturforsch.*, 1947, **20**, 258.

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375. *The Interaction of Metal Chlorides with Organic Chlorides. Part II.* Electrochemical Studies on Solutions of Titanium Tetrachloride in Some Alkyl Chlorides.*

By W. R. Longworth and P. H. Plesch.

The specific conductivity κ of titanium tetrachloride and of its solutions in benzene and various alkyl chlorides was measured by using a high-vacuum technique. For solutions in methylene dichloride and ethyl chloride at 0° κ is of the order of 10^{-7} mho cm.$^{-1}$ and goes through a marked maximum near $[TiCl_4] = 0{\cdot}4$M. The conductivity is ascribed to a self-ionisation $2TiCl_4 \rightleftharpoons TiCl_3^+ + TiCl_5^-$, of which the equilibrium constant in both solvents at 0° is of the order of 10^{-16}—10^{-18}, and falls approximately exponentially with increasing concentration of titanium tetrachloride. Our interpretation is supported by electrolyses in which titanium trichloride was deposited on the cathode. The decrease in κ with increasing concentration of titanium tetrachloride is ascribed to the concurrent decrease in the dielectric constant of the solutions.

The results of other authors on the conductivity of solutions of aluminium bromide and of the methylaluminium bromides in alkyl bromides have been reinterpreted in terms of self-ionisation.

The interaction of metal halides with alkyl halides is of wide interest, not least because of the possible formation of ions in such systems. This feature is of particular interest in connection with Friedel–Crafts reactions and cationic polymerisations. The evidence most frequently quoted in support of the ionisation of alkyl halides by metal halides is the work of Wertyporoch [1] on the conductivity of solutions of aluminium bromide in ethyl bromide. However, a re-examination of this system by Fairbrother and Scott [2] under rigorously dry conditions showed that the electrical conductivity is due to a self-ionisation of the aluminium bromide; our re-interpretation of their results supports this conclusion. Further support for the idea of a general ionogenic reaction between metal halides and alkyl halides appeared

* Part I, *J.*, 1958, 451.
[1] Wertyporoch, *Ber.*, 1931, **64**, 1369, and others.
[2] Fairbrother and Scott, *J.*, 1955, 452.

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to be provided by the formation of triphenylmethyl cations from triphenylmethyl halides and metal halides.[3,4,5]

The reactions in question can be represented by the equilibrium

$$RX + MX_n \rightleftharpoons R^+MX_{n+1}^-$$

Since the position of the equilibrium is governed by the free-energy change, and the entropy changes will be relatively small, we can consider the matter in terms of the enthalpy change. Thus,

$$\Delta H = D(R\text{–}X) - I(R) + E(X) - D(MX_n\text{–}X^-) - \Delta H_s(R^+MX_{n+1}^-) + \Delta H_s(RX) + \Delta H_s(MX_n) - e^2/r$$

The D's are bond-dissociation energies, $I(R)$ is the ionisation potential of radical R, $E(X)$ the electron-affinity of atom X, and the ΔH_s's are heats of solvation; the term e^2/r represents the Coulombic energy of the ion-pair. The first three terms can conveniently be represented by the heterolytic bond-dissociation energy

$$\theta(R^+\text{–}X^-) = D(R\text{–}X) - I(R) + E(X).$$

Variations in the nature of the alkyl halide RX will affect all the ingredients of ΔH, but especially θ, which ranges from 230 kcal./mole for methyl chloride to about 115 kcal./mole for triphenylmethyl bromide. It is, therefore, evident that the extent of ionogenesis will vary widely and that argument by qualitative analogy may be very misleading.[6] One can understand in these terms the apparent absence of ionisation which H. C. Brown and his collaborators found in various metal halide–alkyl halide systems.[7] Our own results [8] on the binary freezing-point phase diagrams of titanium tetrachloride with various alkyl chlorides also gave no evidence for any such interaction. In the present work we studied the conductivity of titanium tetrachloride in a number of alkyl chlorides and in benzene, in a further attempt to detect and, if possible, to identify any ions present. This is of particular interest to us in connection with current theories of cationic polymerisation, especially in relation to the cocatalytic activity of alkyl halides with metal halide catalysts.[9,10,11]

Experimental

Materials.—Alkyl chlorides and titanium tetrachloride were purified as described.[8] Benzene was purified and dried by conventional methods and then over calcium hydride, fractionally distilled, fractionally crystallised twice, and fractionated once in the vacuum system by bulb-to-bulb distillation.

Apparatus.—The conductivity cell of Pyrex glass, closely similar to Fairbrother and Scott's,[2] was fitted with bright platinum electrodes, 1·5 × 1·5 cm., 1·5 mm. apart, sealed through soda-glass and graded seals, and contained a glass-enclosed magnet for stirring. The cell constant (by KCl calibration) was 0·053. The resistance of the solution did not vary with the quantity of solution in the cell provided this exceeded 12 ml.

Operation.—The cell was fused to a high-vacuum system without joints or greased taps, thoroughly flamed, pumped, flushed with titanium tetrachloride vapour, and pumped again, before each series of measurements. The titanium tetrachloride and the alkyl chloride or benzene were distilled into the cell, and the concentrations computed as described.[8] When the required mixture had been distilled in, the cell was brought to constant temperature in melting ice, and the resistance measured; the contents were stirred magnetically.

[3] Fairbrother and Wright, *J.*, 1949, 1058.
[4] Evans *et al.*, *J.*, 1955, 206, 3104; 1957, 1020.
[5] Porter and Baughan, *J.*, 1958, 744.
[6] Burton and Praill, *Quart. Rev.*, 1952, **6**, 302.
[7] Brown *et al.*, *Ind. Eng. Chem.*, 1953, **45**, 1462.
[8] Longworth, Plesch, and Rigbi, *J.*, 1958, 451.
[9] Pepper, *Trans. Faraday Soc.*, 1949, **45**, 397.
[10] Plesch, *J.*, 1953, 1662.
[11] Colclough and Dainton, *Trans. Faraday Soc.*, 1958, **54**, 901.

Resistance measurements were made, at 1000 c./sec., by a Wheatstone bridge using a cathode ray oscilloscope as visual null-point indicator, as described by Haszeldine and Woolf.[12] Both resistance and capacity out-of-balance were indicated separately. The discrimination for resistances of the order of 100,000 ohms was 1 part in 1000. The smallest measurable conductivity was 10^{-8} mho cm.$^{-1}$. Each reading was checked over a period of 15 min. and, if constant, was recorded; if the resistance drifted, further readings were taken until it was constant.

Results

Conductivity Experiments.—All the recorded observations except those with benzene were made on colourless solutions of titanium tetrachloride, and colour was used as a criterion of purity, because a faint yellow colour was found to indicate a leak in the vacuum system. All benzene solutions of titanium tetrachloride were yellow because of the binary complex which is formed.[13]

Pure Materials.—The conductivities of pure titanium tetrachloride, carbon tetrachloride, chloroform, methylene dichloride, ethyl chloride, and benzene were not detectable.

Titanium tetrachloride in carbon tetrachloride, chloroform, and benzene. The conductivities of solutions of titanium tetrachloride in carbon tetrachloride, chloroform, and benzene at 0°, containing up to 1 mole/l. of titanium tetrachloride, could not be detected, and there was no change after several hours at ambient temperatures.

Table 1. *Specific conductivity (in mho cm.$^{-1}$) of titanium tetrachloride solutions at 0° (molar concns.).*

In methylene dichloride				In ethyl chloride					
Series 1		Series 2		Series 1		Series 2		Series 3	
$[TiCl_4]$	$10^8\kappa$	$[TiCl_4]$	$10^8\kappa$	$[TiCl_4]$	$10^7\kappa$	$[TiCl_4]$	$10^7\kappa$	$[TiCl_4]$	$10^7\kappa$
0·19	5·26	0·06	6·20	0·30	4·48	0·10	0·84	0·63	4·30
0·62	7·64	0·13	7·12	0·37	4·68	0·23	3·46	0·88	3·40
1·20	6·74	0·23	7·75	0·47	4·76	0·38	4·64	1·06	2·54
1·63	5·84	0·37	8·00	0·57	4·48	0·50	4·72		
2·03	4·78	0·64	8·23	0·66	3·72	0·63	4·16		
2·48	3·68	1·15	7·12						

Methylene dichlorides. All solutions of titanium tetrachloride in methylene dichloride were stable for up to 6 hr. Two separate series of experiments gave the results shown in Table 1 and plotted in Fig. 1 (curve *A*).

Ethyl chloride. All solutions of titanium tetrachloride in ethyl chloride were stable; during 6 hr., the approximate duration of the experiments, the conductivity changed by less than 10%. The results obtained in three series of experiments with different batches of materials are shown in Table 1 and plotted in Fig. 1 (curve *B*).

Ethyl chloride–carbon tetrachloride mixtures. In order to examine the effect of dielectric constant on conductivity, measurements were made on mixtures of titanium tetrachloride, ethyl chloride, and carbon tetrachloride in which the concentration of titanium tetrachloride was kept constant and that of carbon tetrachloride increased. The results are shown in Table 2.

Table 2. *Specific conductivity of titanium tetrachloride in mixtures of ethyl chloride and carbon tetrachloride at 0°.*

	A					B		
$[TiCl_4]$ (mole/l.)	0·33	0·33	0·44	0·44	0·44	0·44	0·42	0·406
Volume (%) of CCl_4	4·80	7·00	0	4·76	6·92	6·92	10·00	12·92
Volume (%) of total tetrachlorides	8·45	10·50	4·76	9·53	11·60	11·60	14·50	17·30
$10^7\kappa$ (mho cm.$^{-1}$)	4·20	3·87	5·00	4·31	3·74	3·74	2·78	2·28

A further series in which the concentration of titanium tetrachloride was reduced by successive additions of carbon tetrachloride is shown in Table 2 and Fig. 1*C*.

Electrolyses.—These were carried out at ambient temperatures with a cell of Pyrex glass fitted with two bright platinum electrodes, 1 cm. in diameter and 2·5 cm. apart, with a potential

[12] Haszeldine and Woolf, *Chem. and Ind.*, 1950, 544.
[13] Cullinane, Chard, and Leyshon, *J.*, 1952, 4106.

difference of 1000 v. During the electrolysis the cell was kept in the dark because of the reported effect of light on the solutions.[8] The cell was fused to the high-vacuum system and filled as described for the conductivity cell. The current was measured by a microammeter with 20 μA divisions.

With 20 ml. of a 0·4M-solution of titanium tetrachloride in methylene dichloride, the current started at 60 μA and had fallen to approximately 10 μA after 1 hr. After 4 hr. a bronze-coloured deposit was formed on the cathode while the anode remained bright and clean. After 30 hr. the current had dropped to less than 1 μA; the colour of the deposit had darkened and dark violet crystals could be seen growing from the cathode; the anode remained clean but became slightly pitted. This growth of crystals on the cathode continued as long as the current was passed, which was 20 days. The progressive fall in the current was presumably due to the coating on the cathode. Because of the small current, a chemical analysis of the fluid cell

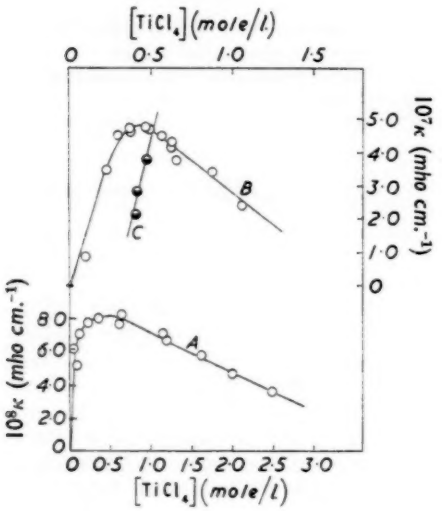

FIG. 1. *Specific conductivity* κ *of solutions of* $TiCl_4$ *in*: A, CH_2Cl_2; B, EtCl; C, *a mixture of* EtCl *and* CCl_4.

contents did not appear promising. A comparative mass-spectrometric analysis of the washed and dried fluid and of a fresh specimen of the same batch of methylene dichloride showed them to be identical and to contain no impurities in quantities greater than a few parts per 100,000. Analysis of the deposit on the cathode showed it to be titanium trichloride.

A similar experiment was carried out with 20 ml. of a 0·47M-solution of titanium tetrachloride in ethyl chloride. The current started at 550 μA and had fallen to about 90 μA after 1 hr. The electrolysis was continued for 12 days, at the end of which the current had fallen to about 2 μA. The appearance of the brownish-purple deposit on the cathode was similar to that formed in the experiment with methylene dichloride. Analysis of the deposit showed it to consist of 0·048 mole of titanium trichloride. The fluid cell contents were not analysed. Integration of the current–time curve showed that a quantity of electricity equivalent to 0·054 mole had been passed through the cell. However, because of the relative crudeness of the microammeter this figure cannot be regarded as very reliable.

DISCUSSION

Conductivity Curves.—The absence of any measurable conductivity in pure titanium tetrachloride and in its solutions in benzene and carbon tetrachloride was to be expected and requires no comment; the absence of conductivity in the chloroform solutions will be discussed below. The very marked maximum in the specific conductivity curves for the methylene dichloride and ethyl chloride solutions appears to be a new phenomenon for which we have found no close analogue in the literature.

The explanation of these curves requires the answering of two questions: what is the ionogenic reaction, and what are the influences which produce the variation of specific conductivity with concentration of titanium tetrachloride?

The hypothetical ionogenic reaction of the metal chloride with the solvent

$$TiCl_4 + RCl \rightleftharpoons R^+ + TiCl_5^- \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

cannot account for the observations, since it implies that the total concentration of ions, and therefore also the specific conductivity, varies with the square-root of the titanium tetrachloride concentration, which is not in agreement with our results. Nor does the combination of equilibrium (i) with others involving ion-pairs and -triplets, and complex ions, such as $Ti_2Cl_9^-$, lead to the required results.

The only other plausible ionogenic reaction is a self-ionisation, such as *

$$2TiCl_4 \rightleftharpoons TiCl_3^+ + TiCl_5^- \quad (K) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (ii)$$

This implies a linear relationship between specific conductivity and concentration and thus represents the initial parts of our curves, but by itself it cannot account for the maximum. We have examined combinations of equilibrium (ii) with a large number of others without finding any plausible system of equilibria which would give a maximum in the conductivity curve, even taking into consideration the smaller ionic conductivities of large complex ions.

We are thus driven to seek the origin of the phenomenon in effects other than the existence of a multiplicity of equilibria. The most obvious feature is the reduction in the dielectric constant (D.C.) of the systems with increasing concentration of titanium tetrachloride. We are aware of the fact that the macroscopic D.C. of a liquid—and even more so of a mixture of liquids—is not an adequate measure of its solvating properties, and thus of its influence on ionogenic and ionic equilibria. However, it is the only simple and readily available property which can be used at present. The effect of varying D.C. on the conductivity can be separated into two components: in view of the low D.C. of all our solutions, the equilibrium (ii) must be the net result of an ionogenic equilibrium

$$2TiCl_4 \rightleftharpoons TiCl_3^+TiCl_5^- \quad (K_1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (iii)$$

giving ion-pairs, and a dissociation equilibrium of the ion pairs:

$$TiCl_3^+TiCl_5^- \rightleftharpoons TiCl_3^+ + TiCl_5^- \quad (K_2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (iv)$$

The influence on K_1 and K_2 of the change in D.C. with changing concentration of titanium tetrachloride can be analysed as follows:

From the equilibria (iii) and (iv) it follows that

$$\begin{aligned} \kappa &= \lambda_3[TiCl_3^+] + \lambda_5[TiCl_5^-] \\ &= (\lambda_3 + \lambda_5)K_1^{\frac{1}{2}}K_2^{\frac{1}{2}}[TiCl_4] \end{aligned}$$

The *true* ionic conductivity is

$$\Lambda_T = (\lambda_3 + \lambda_5) = 2\kappa/c$$

where c is the *total* concentration of *free* ions. Denoting $[TiCl_4]$ by a, we obtain

$$\kappa = \Lambda_T K_1^{\frac{1}{2}}K_2^{\frac{1}{2}}a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

Hence

$$\frac{d \ln \kappa}{da} = \frac{d \ln \Lambda_T}{da} + \tfrac{1}{2}\frac{d \ln K_1K_2}{da} + \frac{1}{a}$$

* Another, and perhaps more plausible, equilibrium is $3TiCl_4 \rightleftharpoons 2TiCl_3^+ + TiCl_6^{2-}$. This also yields a linear relationship between κ and the concentration of titanium tetrachloride, analogous to eqn. (1), so that the available information does not enable us to discriminate between the two modes of ionisation; for simplicity we shall interpret our results in terms of equilibrium (ii): the matter could be decided by transport experiments.

The Λ_T depends on a principally through the viscosity η, and K_1 and K_2 depend on a through the D.C.(ε). If we express the variation of η and of ε with a by the linear relationships

$$\eta = \eta_0 + \gamma a \quad \text{and} \quad \varepsilon = \varepsilon_0 - \beta a \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

we obtain

$$\mathrm{d}\eta/\mathrm{d}a = \gamma \quad \text{and} \quad \mathrm{d}\varepsilon/\mathrm{d}a = -\beta$$

Thus

$$\frac{\mathrm{d}\ln\kappa}{\mathrm{d}a} = \frac{1}{a} + \gamma\frac{\mathrm{d}\ln\Lambda_T}{\mathrm{d}\eta} - \frac{\beta}{2}\frac{\mathrm{d}\ln K_1K_2}{\mathrm{d}\varepsilon} \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

Since Walden's rule holds to a good approximation in most systems of the kind which are under consideration here,

$$\mathrm{d}\ln\Lambda_T/\mathrm{d}\eta = -1/\eta = -1/(\eta_0 + \gamma a) \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

Thus

$$\frac{\mathrm{d}\ln\kappa}{\mathrm{d}a} = \frac{1}{a} - \frac{\gamma}{\eta_0 + \gamma a} - \frac{\beta}{2}\left(\frac{\mathrm{d}\ln K_1}{\mathrm{d}\varepsilon} + \frac{\mathrm{d}\ln K_2}{\mathrm{d}\varepsilon}\right) \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The second term on the right of equation (5) can be written as $1/(a + \eta_0/\gamma)$ and is thus seen to be positive and smaller than the first term, so that the sum of the first two terms is positive. Regarding the third term, both theory and experiment show that equilibrium constants of the type of K_1 and K_2 fall very rapidly with decreasing D.C., and that, moreover, the rate of change increases with falling D.C. The third term is, therefore, positive, and it is an increasing function of a since the D.C. ε decreases with increasing a. Thus eqn. (5), and, therefore, also the κ–a curves, must have a maximum, and eqn. (5) is, therefore, at any rate in qualitative accord with our observations.

The effect of D.C. on conductivity is perhaps most strikingly illustrated by the results in Table 2*A*, and Fig. 2*C*. The addition of carbon tetrachloride at constant titanium tetrachloride concentration produces a drastic reduction in the conductivity. Moreover, as shown by the results of Table 2*B* and Fig. 1*C*, when the titanium tetrachloride concentration is reduced progressively by the addition of carbon tetrachloride the fall in the conductivity is far steeper than can be accounted for by the simple dilution effect in the binary system.

The variation of conductivity with D.C. can be evaluated from equations (1), (2), and (4), and is conveniently represented by

$$\frac{\mathrm{d}\ln(\kappa/a)}{\mathrm{d}\varepsilon} = \frac{\mathrm{d}\ln\Lambda_T}{\mathrm{d}\varepsilon} + \tfrac{1}{2}\frac{\mathrm{d}\ln K}{\mathrm{d}\varepsilon}$$

$$= \frac{1}{\beta(a + \eta_0/\gamma)} + \tfrac{1}{2}\frac{\mathrm{d}\ln K}{\mathrm{d}\varepsilon} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6a)$$

$$= \frac{1}{\varepsilon_0 - \varepsilon + \beta\eta_0/\gamma} + \tfrac{1}{2}\frac{\mathrm{d}\ln K}{\mathrm{d}\varepsilon} \quad . \quad . \quad . \quad . \quad . \quad . \quad (6b)$$

where $K = K_1K_2$. Our results are shown as plots of log (κ/a)against $1/\varepsilon$ in Fig. 2. The D.C. of the solutions were computed by assuming a linear dependence on concentration, and using the following values for the D.C. of the pure substance at 0°: CH_2Cl_2 9·93,[14] C_2H_5Cl 12·25,[15] $TiCl_4$ 2·80,[14] CCl_4 2·28.[14] Since the first term of eqn. (6) varies only very slowly with ε, the very rapid variation of κ with D.C. is evident.

[14] National Bureau of Standards, Circular 514.
[15] Longworth and Plesch, *J.*, 1959, 1618.

Since the D.C. of chloroform at 0° is relatively low (5·21), our inability to detect a measurable conductivity for solutions of titanium tetrachloride in this solvent is in conformity with our other results.

The composite equilibrium constant of equilibrium (ii), $K = K_1K_2$, can be estimated as follows: Λ_T can be estimated to be of the order of 100 for both solvents. If $\kappa/a = 10^{-6}$, it follows from eqn. (1) that K is of the order of 10^{-16}. The limiting value of K at $a = 0$ is of the order of 10^{-18} for methylene dichloride and 10^{-16} for ethyl chloride.

It should be noted that in these systems Λ_T *cannot* be derived from the limiting value of κ/a unless K is measured by an independent method.

Electrolysis.—Our theory of self-ionisation suggests that, if the solutions are electrolysed, titanium trichloride should be deposited at the cathode. This has been confirmed qualitatively, and a semi-quantitative experiment has shown that at any rate the major portion of the current is carried in this manner. The fate of the chlorine which must be liberated at the anode is unknown. It is noteworthy that our electrolytic preparation of titanium

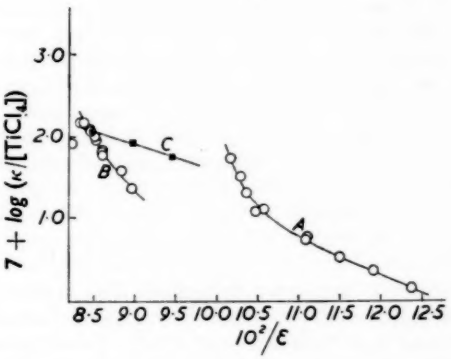

FIG. 2. *Plot of* log $(\kappa/[TiCl_4])$ *against the reciprocal of the dielectric constant* ε. *Curve* A, *in* CH_2Cl_2; *curve* B, *in* EtCl; *curve* C, *in mixtures of* EtCl *and* CCl_4. (For curve *C*, $[TiCl_4] = 0{\cdot}44$ mole/l.)

trichloride provides one of the very few examples of a polyatomic ion being deposited intact upon discharge at an electrode.

Conclusion.—The results give no indication of an ionogenic reaction between titanium tetrachloride and methylene dichloride or ethyl chloride. The observed conductivities can be interpreted by a self-ionisation of the titanium tetrachloride, the extent of which depends strongly on the dielectric constant of the solution.

Ionisation of Aluminium Bromide.—Only very few studies have been made of simple systems analogous to ours, *i.e.*, consisting of metal halide and alkyl halide only, and most of these are vitiated by failure adequately to exclude moisture. Fairbrother and Scott's results [2] on the system aluminium bromide–ethyl bromide promised to provide an interesting comparison with our work. We re-examined their conductivity data and found that the specific conductivity is accurately proportional to the square of the concentration of aluminium bromide. If it be assumed that there is only one type of cation and of anion, and these be represented by A^+ and A^- in order not to prejudice the question of their nature, and if c is the *total* concentration of free ions, then

$$\kappa = \lambda_+[A^+] + \lambda_-[A^-] = \tfrac{1}{2}\Lambda_T c$$

Λ_T is the *true* ionic conductivity, and not the quantity $\Lambda = \kappa/[AlBr_3]$ used by the original authors which—in view of the very low degree of ionisation—has little, if any, significance. Since κ is proportional to c, it follows that for this system c must be proportional to the square of the aluminium bromide concentration. An examination of all plausible

equilibria, including those favoured by the original authors, showed that the only one which would yield this relationship is

$$4AlBr_3 \rightleftharpoons (AlBr_3)_xAlBr_2^+ + (AlBr_3)_{3-x}AlBr_4^-$$

If $x = 1$

$$4AlBr_3 \rightleftharpoons Al_3Br_5^+ + Al_3Br_7^-$$

and

$$K = \frac{[Al_3Br_5^+][Al_3Br_7^-]}{[AlBr_3]^4} \approx \frac{c^2}{4[AlBr_3]^4}$$

It follows that

$$\kappa = \tfrac{1}{2}\Lambda_T c = \Lambda_T K^{\frac{1}{2}}[AlBr_3]^2$$

and from the slope of the plot of κ against $[AlBr_3]^2$, we find $\Lambda_T K^{\frac{1}{2}} = 1{\cdot}44 \times 10^{-4}$. If we assume that Λ_T is of the order of 100 mho cm.^{2} mole^{-1}, we obtain $K = 2 \times 10^{-18}$ l.^{2} mole^{-2} at 25°. The greater mobility of the anion reported by Fairbrother and Scott may be due to the cation's being more strongly solvated than the anion, or x may be greater than unity. Thus Fairbrother and Scott's conclusion, that the conductivity of aluminium bromide in ethyl bromide is due to self-ionisation, is valid but this self-ionisation probably occurs in a manner different from that originally suggested. Dr. Fairbrother has authorised us to state that he concurs with our views as preferable to his original interpretation.

An analysis of Jacober and Kraus's results [16] along the same lines shows that at 0° in methyl bromide solution the specific conductivities of aluminium bromide and of methylaluminium dibromide are accurately proportional to the square of the concentration, and that for dimethylaluminium bromide the specific conductivity is proportional to the fourth power of the concentration. The specific conductivities found by Jacober and Kraus are much higher than those of Fairbrother and Scott, and the plots of their results make relatively large intercepts on the conductivity axis; this indicates that their work may have been strongly affected by impurities, so that an evaluation of equilibrium constants from it is probably not warranted. The very high degree of complexity of the ions formed from the dimethylaluminium bromide which is suggested by these results is noteworthy.

The absence of any obvious dielectric effect in these systems, in contrast to our own, is most probably due to the fact that they cover a smaller concentration range and, more important, that the D.C. of aluminium bromide is appreciably greater than that of titanium tetrachloride; extrapolation indicates a D.C. of about 3·7 for the hypothetical supercooled liquid at 0°.

[*Added, April 1st*, 1959.—Conductivity maxima similar to those in Fig. 1 were obtained by Greenwood and Martin (*J.*, 1953, 757) with the system boron fluoride–methanol, and by Payne (Proc. International Conference on Co-ordination Compounds, Amsterdam, 1953, p. 75) with the system titanium tetrachloride–phosphoryl chloride. These authors did not attempt to explain the maxima, but it is evident that the dielectric constant effect suggested by us will also explain their results.]

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KEELE, STAFFORDSHIRE. [*Received, December 8th*, 1958.]

[16] Jacober and Kraus, *J. Amer. Chem. Soc.*, 1949, **71**, 2405.

376. *The Uptake of Three Drugs by* Bact. lactis aerogenes.

By P. J. Stoward.

The uptake of three drugs by sensitive and resistant strains of *Bact. lactis aerogenes* has been studied as a function of equilibrium drug concentration.

Sensitive and non-sensitive strains took up equal amounts of Brilliant Green, while a strain resistant to Crystal Violet took up more of that drug than the corresponding sensitive strain.

On the other hand, the uptake observed for 2 : 4-dinitrophenol was small at a neutral pH, but was increased at a pH below the isoelectric point of the bacterial surface.

The significance of these results is discussed in terms of permeability and other theories of drug resistance.

It is often considered that organisms resistant to the action of drugs are less permeable towards the drug than their sensitive counterparts. The resistance of trypanosomes, for example, to parafuchsin and acridines [1] and to a wide range of arsenical compounds [2] has been shown to be due to a loss in permeability towards the inhibitor. Similarly, normal relapsing-fever spirochætes absorb arsenic and gold from neoarsphenamine and solganol respectively, whereas the resistant forms absorb neither element.[3]

On the other hand, previous work in this laboratory and elsewhere [4] has indicated that drug-resistant strains of bacteria may sometimes take up the same amount of drug as non-resistant strains, or even more.

The contrast of these various results suggested that more experimental results should be obtained before general correlations between drug response and permeability are looked for.

In this paper, the uptake per cell of three drugs, two cationic and one anionic, by drug-resistant and sensitive forms of the gram-negative coliform organism *Bact. lactis aerogenes* has been measured as a function of the equilibrium concentration in the supernatant liquid. No distinction will be made between drug adsorbed on to the bacterial surface and that absorbed into the cell interior. The experimental curves, which may be simply termed absorption isotherms, serve, however, to show any differences in the amount taken up by the drug-resistant and the sensitive strains.

Experimental

The strain of *Bact. lactis aerogenes* was maintained by subculture monthly in " Lemco " broth, and daily in a standard minimal medium made up by mixing the following solutions: 10 ml. of glucose (50 g./l.); 10 ml. of phosphate buffer ($Na_2HPO_4,12H_2O$, 16 g./l.; KH_2PO_4, 2·96 g./l.; pH 7·1); 5 ml. of aqueous ammonium sulphate (5 g./l.); 1 ml. of a solution containing magnesium sulphate ($MgSO_4,7H_2O$, 1 g./l.) and ferrous sulphate (5·2 mg./l.).

By repeated subculture of this strain into the standard minimal medium containing drug at increasing concentrations, resistant strains were obtained which were able to grow at a concentration ($\bar{m}$) many times that originally inhibitory to growth. In this way, strains were made resistant to Brilliant Green ($\bar{m} = 2000$), Crystal Violet ($\bar{m} = 40$), and 2 : 4-dinitrophenol ($\bar{m} = 1500$).

The Crystal Violet and 2 : 4-dinitrophenol used in the training experiments were dissolved in phosphate buffer. The pH of the dinitrophenol solution was adjusted to 7 by the addition of a few drops of concentrated sodium hydroxide. The appropriate amount was then added to the standard minimal medium in place of part or all of the 10 ml. of phosphate buffer so as to obtain the final concentration.

[1] Fischl and Singer, *Z. Hygiene Infektionskrankheiten*, 1934, **116**, 138.
[2] Hawking, *J. Pharmacol.*, 1937, **59**, 123.
[3] Fischl, Kobtra, and Singer, *Z. Hygiene Infektionskrankheiten*, 1934, **116**, 69.
[4] Dean and Hinshelwood, Ciba Foundation Symposium on Drug Resistance in Micro-organisms, 1957, pp. 4—24.

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Bacterial population densities were measured with the aid of a Hilger Spekker light absorptiometer, calibrated against the microscope count of actual numbers of bacteria made in a hæmocytometer counting chamber.

Absorption Experiments.—Preparation of the cell suspension before an absorption experiment required care if consistent results were to be obtained. Two l. of bacterial culture, previously freed from any drug by one subculture in a standard minimal medium, were grown and taken off towards the end of the logarithmic phase. The cells were separated from the growth medium by centrifugation at 3000 r.p.m. for ~5 min. After being washed with saline solution (9 g./l.), the cells were resuspended and stored overnight in more saline solution.

When needed for an experiment, the suspension was recentrifuged and the cells were resuspended in phosphate buffer (or saline) after being washed with more buffer solution. The concentration of the bacterial suspension was adjusted until the count was $2—4 \times 10^9$ cells per ml.

Portions of this suspension were pipetted into dry boiling tubes. Varying volumes of an accurately prepared drug solution and phosphate buffer solution (or saline) were added so that the final volume in each tube was the same. All pipettes used had been recalibrated. When thick suspensions were used, the finite volume of the cells was taken into account, on the assumption that 10^{11} cells occupy 0·1 ml.[5]

The suspensions were then allowed to come to equilibrium in a thermostat at 25°, purified air being bubbled slowly through the suspension.

After ~30 min., the tubes were removed and their contents centrifuged for ~10 min. and pipetted off, and the final drug concentrations estimated. Sometimes an appreciable quantity of a slimy layer was formed during the experiments, but often most of this polysaccharide could be packed down and a clear supernatant left by longer centrifuging.

The amount of drug taken up (A_s) was calculated from the equation $A_s = V(m_o - m_f)/n_s v$, where v is the volume of the bacterial suspension used, n_s its count, V the total volume of the system, m_o and m_f the initial and the residual drug concentrations respectively. A plot of A_s against m_f represents the absorption isotherm.

Results and Discussion

The use of the quantity A_s differs a little from the approach adopted by other workers. Absorptiometer counts are proportional to bacterial mass. Peacocke and Hinshelwood[6] used actual cell numbers from hæmocytometer counts. On the other hand, absorption has sometimes been expressed as the amount taken up per unit dry mass of bacteria.[5,7,8] So long, however, as the average size of the cells does not vary significantly, the different methods correspond, and the absorptiometer readings are easy and fast.

The units were such that A_s is expressed as g. of the drug taken up by 10^{15} cells. Since $2·6 \times 10^{10}$ cells weigh approximately 30 mg.,[9] the numerical results stated in this paper can be compared with others differently expressed.

(1) *Brilliant Green.*—Difficulties were met at first in the colorimetric determination of Brilliant Green; the optical density of a sample increased with time after dilution of a given stock solution. Variations also occurred when different stock solutions were used. Now, the coloured cation of Brilliant Green is unstable and isomerises to a colourless and feebly basic carbinol.[10] The equilibrium took some time to establish, but the optical density of a solution freshly diluted with saline solution reached a sensible maximum after 90 minutes. Fry[11] fixed the equilibration time arbitrarily as one hour.

Since different stock solutions gave different calibration curves, a new curve was prepared for each absorption experiment. Standard samples from a freshly prepared stock solution were taken through the same operations as the test solutions used in the

[5] Peacocke, *Exp. Cell Res.*, 1954, **7**, 498.
[6] Peacocke and Hinshelwood, *J.*, 1948, 2290.
[7] Newton, *J. Gen. Microbiol.*, 1954, **10**, iii.
[8] Few and Schulman, *ibid.*, 1953, **9**, 454.
[9] Dean, 1958, personal communication.
[10] Goldacre and Phillips, *J.*, 1949, 1724.
[11] Fry, *J. Gen. Microbiol.*, 1957, **16**, 341.

absorption experiments. At the end of a run, the supernatant solutions and the standards were diluted with saline solution until the concentration of the dye was within the range 0—20 mg./l. Their optical densities were measured 90 minutes later in a 0·5 cm. optical glass cell at 630 mμ in a SP. 600 Unicam Spectrophotometer.

Since the aim of the experiment was to compare the sensitive and the resistant strain, the following method was used. Separate concentrated suspensions (2 ml.) of the sensitive ($\bar{m} = 0$) and the resistant strain ($\bar{m} = 2000$) were added in parallel tubes containing 10 ml. of drug solution and saline. When equilibrium was reached, the solutions were centrifuged. The supernatant liquors were diluted and the colour was estimated after the time needed for the complex carbinol equilibria to readjust themselves.

The results (Fig. 1) indicate that the sensitive and the resistant strains take up the same amount of Brilliant Green. The general shape of the curve conforms approximately to a Langmuir type of adsorption isotherm particularly in the lower concentration range.

(2) *Crystal Violet.*—The general technique described above was used. Drug concentrations were measured colorimetrically at 590 mμ. A correction for the adsorption of the dye by the walls of the centrifuge tube was made (1·5 mg./l. for the volumes used).

FIG. 1. *The uptake of Brilliant Green by* Bact. lactis aerogenes *at* pH 7.

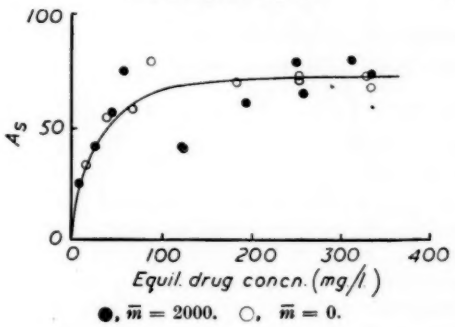
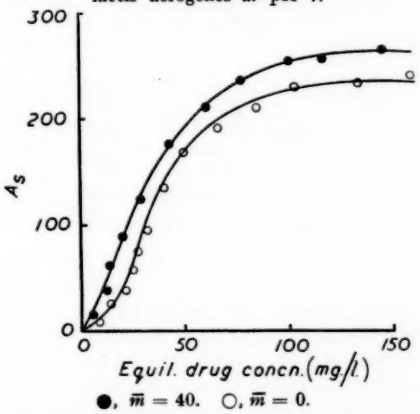


FIG. 2. *The uptake of Crystal Violet by* Bact. lactis aerogenes *at* pH 7.



The experimental curves (Fig. 2) clearly show that the resistant strain ($\bar{m} = 40$) takes up more Crystal Violet than the sensitive strain. The maximum values of A_s were reached when the supernatant concentration was about 100 mg./l. The sensitive strain gave a maximum value of A_s of 230—240 units; the corresponding non-sensitive strain gave one of 260 units.

A distinctive feature of the curves is their sigmoid shape, somewhat reminiscent of the isotherms found for the adsorption of certain gases on solids [12] and proflavine on *Bact. lactis aerogenes*.[6] This can be attributed partly to a co-operative effect in which the presence of adsorbed molecules helps the adsorption of more drug on to neighbouring sites.

(3) 2 : 4-*Dinitrophenol.*—Preliminary experiments indicated that the uptake of drug would be very small. Large volumes of a concentrated bacterial suspension were therefore used.

When equilibrium between 10 ml. of suspension and 5 ml. of drug solution had been established, the solution was centrifuged and the optical density of the supernatant liquor, after suitable dilution with phosphate buffer (pH 7), was estimated at 395 mμ in a 1 cm. cell.

The results (Fig. 3) show that the uptake at pH 7 is small. It has often been stated,

[12] Drain, *Sci. Progr.*, 1954, **42**, 608.

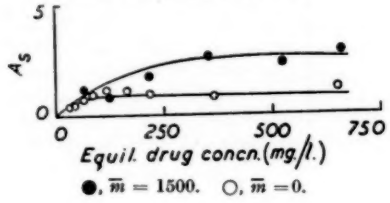
however, that bacteria will only adsorb anionic substances at a pH below the isoelectric point of the bacterial surface. This suggested that there might be a possibility that the uptake of drug would be increased at pH 4—5 if the isoelectric point of gram-negative organisms is about 4·3.

A phosphate buffer (990 ml. of a solution containing 9·08 g./l. of KH_2PO_4 and 10 ml. of a solution of 23·88 g./l. of $Na_2HPO_4,12H_2O$) was used for the experiment at pH 5. The buffer of pH 4 was made up from potassium hydrogen phthalate (10·2 g./l.). The results are plotted in Fig. 4.

At a pH above the isoelectric point, the resistant strain ($\bar{m} = 1500$) probably took up slightly more drug than the corresponding sensitive strain ($\bar{m} = 0$). Below the isoelectric point, on the other hand, the sensitive strain took up a little more than the non-sensitive strain. Both strains picked up 2—3 times as much drug at pH 4 as at a pH near neutrality.

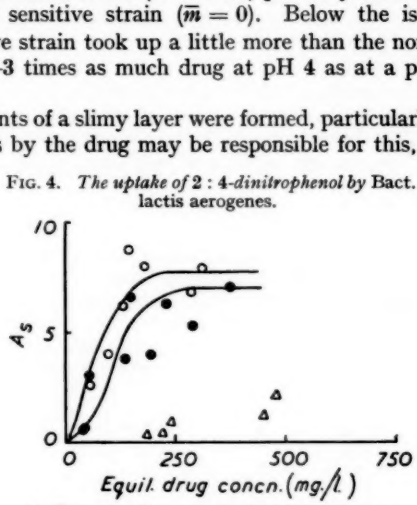
During the experiments, appreciable amounts of a slimy layer were formed, particularly in the acid solutions. Some lysis of the cells by the drug may be responsible for this, a

FIG. 3. *The uptake of* 2 : 4-*dinitrophenol by* Bact. lactis aerogenes *at* pH 7.



●, $\bar{m} = 1500$. ○, $\bar{m} = 0$.

FIG. 4. *The uptake of* 2 : 4-*dinitrophenol by* Bact. lactis aerogenes.



○, $\bar{m} = 0$, pH = 4. ●, $\bar{m}$ 1500, pH = 4.
△, $\bar{m} = 0$, pH = 5.

fact which might lead to modification of the values for A_s. Because of lysis, the actual number of intact cells would be less than the original number n_s, so that the corresponding value of A_s would need to be increased. Although A_s turned out to be only about 6 units at pH 4, the intact cells at the bottom of the centrifuge tubes were markedly yellow while the slimy layer remained unstained.

Some pharmacologists have suggested that drug response should bear a relation to the amount of covalent or non-ionised form of the drug present in the solution. At pH 4, 2 : 4-dinitrophenol is completely un-ionised, while at pH 7·1 it is about 25% un-ionised (calculated from $pK = 4·10$, given by Flexser, Hammett, and Dingwall [13]). The change in the amount of un-ionised form is roughly proportional to the maximum values of A_s observed at the two different pH values. This correlation is, however, probably fortuitous, as the charge on the bacterial surface also changes.

Conclusion.—According to one view, bacteria may develop a resistance towards drugs by modifying their linked enzyme sequences so as to cope with the new unfavourable environment. In such cases resistant strains might well have at least one part of their cell substance expanded, as compared with the original sensitive strain, and this might explain the increased uptake of proflavine [6] and of Crystal Violet by the respective strains of *Bact. lactis aerogenes*.

There is no reason, however, why one component of the cell should not be increased at the expense of another. Although the gross uptake of Methylene Blue [6] or Brilliant Green is the same on both the sensitive and the resistant forms of *Bact. lactis aerogenes*, the

[13] Flexser, Hammett, and Dingwall, *J. Amer. Chem. Soc.*, 1935, **57**, 2107.

proportions of the various components may have changed in spite of the fact that the total number of negatively charged sites on and within the cell, a factor which determines cationic drug uptake, is the same in both cases.

On the other hand, the small but positive uptake of the anionic drug 2 : 4-dinitrophenol at pH 7 might be due to the diffusion of the drug into the cell interior in such a way that its free concentration in the " protoplasmic fluid " equals that of the surrounding drug medium: the magnitude of the result is of the right order for this hypothesis.

It should not be forgotten that the driving force of any ionic or molecular movement across a cell membrane may come from the actual metabolism of the cell. This suggests that an anionic drug may be taken up only by actively growing cells in a full growth medium. Such a hypothesis is worth testing with bacteria, especially since the drug-resistant strains might exhibit quite different active transport processes. The interrelations of electrochemical and concentration gradients in the dynamics of the living cell are delicately balanced: a reinvestigation of anionic drug uptake might give information about these equilibria.

I thank Professor Sir Cyril Hinshelwood, P.R.S., for his help and patient guidance. I also acknowledge helpful discussions from Drs. A. C. R. Dean and B. J. McCarthy.

PHYSICAL CHEMISTRY LABORATORY, OXFORD. [*Received, December 22nd,* 1958.]

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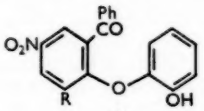
377. ortho-*Hydroxylation of Phenols. Part V.* Dibenzodioxins from Catechols and Analogous Cyclisations.*

By J. D. LOUDON and F. MCCAPRA.

The formation of dibenzodioxins from *o*-nitrophenyl ethers of catechols is reported and correlated with other reactions of similar type.

CATECHOL ETHERS of types (I; R = H and NO_2) are readily prepared by hydroxylation of the corresponding phenyl ethers, or substituted phenyl ethers, and yield the appropriate catechols by ether scission. Piperidine which is an efficient reagent for scission in the mononitro-series was found in the dinitro-series to be less reliable than phenylhydrazine.* This is now shown to be due in part at least to the incidence of cyclisation, *e.g.*, (I; R = NO_2) ⟶ (II), which is promoted by warm piperidine, pyridine, or alkali but is not incurred to any appreciable extent with phenylhydrazine. Presumably the last reagent, by initial attack on the carbonyl centre, provides the opportunity for preferred cyclisation to 5 : 7-dinitro-1 : 3-diphenylindazole with elimination of the catechol residue.



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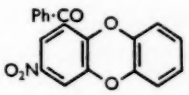

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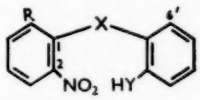
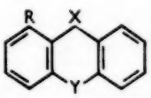
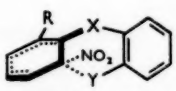


(III)



(IV)



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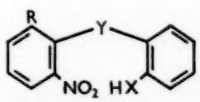


(VI)

Hillyer,[1] using unnecessarily severe conditions, showed that picryl chloride and catechol condense in presence of alkali to form 1 : 3-dinitrodibenzodioxin (as II; NO_2 for Ph·CO),

* Part IV, *J.*, 1954, 1134.

[1] Hillyer, *Chem. Centr.*, 1900, **1**, 723; 1901, **2**, 1121.

the picryl analogue of (I) being undoubtedly an intermediate. This was an extension of Turpin's reaction [2] by which, subject to certain conditions, phenoxazines (IV; X = NH, Y = O) may be obtained by elimination of nitrous acid from an intermediate of type (III). In particular cases analogous cyclisations to phenazines (IV; X = Y = NH),[3] phenoxathiins (IV; X = S, Y = O),[4] and phenothiazines (IV; X = NH, Y = S) [5] are also known. The success of such cyclisations generally depends on the presence of a substituent R in the 6-position of the intermediate (III) and this substituent is usually, but not invariably, a nitro-group or other electron-attracting group. 2-Hydroxy-2′-nitrodiphenylamines are the most extensively examined [6] and it has been suggested that in the absence of the substituent R the conformation of these compounds is fixed by hydrogen-bonding between the amino- and the nitro-group and is thus unfavourable to cyclisation.[6,7] Consistently with this view substitution of the amino-hydrogen atom confers the ability to form phenoxazines even when the substituent R is lacking.[7,8] Hydrogen-bonding however cannot be important for dioxin formation and here we find that picryl chloride, 2-chloro-3 : 5-dinitrobenzophenone, and 1-chloro-2 : 6-dinitrobenzene readily react with catechol in presence of potassium carbonate affording the appropriate dibenzodioxins, whereas 1-chloro-2 : 4-dinitrobenzene does not do so and under forceful conditions yields catechol bis-2 : 4-dinitrophenyl ether by intermolecular reaction. Apparently the presence of a group R in the intermediate (III; X = Y = O) is again an important factor.

These cyclisations may all be described as unoriented nucleophilic substitutions at an aromatic centre. Their prototype is the intermolecular displacement of a nitro-group in 1 : 3 : 5-trinitrobenzene by methoxide ion.[9] Here the nitro-groups, although their (*o* : *p*)-orienting effects are not enlisted, are responsible for attracting the anion and predisposing the system to nucleophilic attack which is complete after a single replacement. In the compounds (III) steric congestion can assist nucleophilic attack (*a*) by inhibiting resonance between a donor group X and the *ortho*-nitrated nucleus, (*b*) by enforcing a conformation which brings the nucleophilic Y into position for alternative attack at centre 1 or 2. The latter course leads *via* the transition state (V) to cyclisation, the former results in a Smiles rearrangement, (III) $\rightleftharpoons$ (VI). This view of the cyclisation is consistent with a range of polar character in the substituent R, it explains the effect of a large group X (*e.g.*, substituted imino) when R is hydrogen, and the relative ineffectiveness of R when transferred to the 6′-position.[6] At the same time it is in harmony with Bunnett's view [10] of the stereochemistry of the Smiles rearrangement, an oriented reaction, in which steric acceleration appears to be maximal when the 6′-position is substituted.

The possibility of Smiles rearrangement in compounds of type (I) where the catechol nucleus is unsymmetrically substituted makes the structures of derived dibenzodioxins ambiguous.[11]

Experimental

3 : 5-*Dinitro*-2-(2 : 3 : 5-*trimethylphenoxy*)*benzophenone*, m. p. 138° (from ethanol), was formed in 80% yield when 2-chloro-3 : 5-dinitrobenzophenone (5 g.) was added portionwise to a solution of 2 : 3 : 5-trimethylphenol (7·5 g.) in pyridine (40 c.c.) and after 15 hr. the whole was poured into dilute sulphuric acid (Found: C, 65·1; H, 4·4. $C_{22}H_{18}O_6N_2$ requires C, 65·0; H, 4·4%).

[2] Turpin, *J.*, 1891, **59**, 722; Ullmann, *Annalen*, 1909, **366**, 79; Ullman and Sané, *Ber.*, 1911, **44**, 3730.
[3] Kehrmann and Kramer, *Ber.*, 1900, **33**, 3078; Kehrmann and Punti, *Ber.*, 1911, **44**, 2622.
[4] Mauthner, *Ber.*, 1905, **38**, 1411; Stevenson and Smiles, *J.*, 1931, 718.
[5] Kehrmann and Steinberg, *Ber.*, 1911, **44**, 3011; Wight and Smiles, *J.*, 1935, 340.
[6] Brady and Waller, *J.*, 1930, 1218.
[7] Roberts and Clark, *J.*, 1935, 1312.
[8] Boothroyd and Clark, *J.*, 1953, 1499.
[9] de Bruyn, *Rec. Trav. chim.*, 1890, **9**, 208.
[10] Okamoto and Bunnett, *J. Amer. Chem. Soc.*, 1956, **78**, 5357, 5363; Bunnett, *Quart. Rev.*, 1958, **12**, 12.
[11] Part II, Loudon and Scott, *J.*, 1953, 265.

2-(2-*Hydroxy*-3 : 5 : 6-*trimethylphenoxy*)-3 : 5-*dinitrobenzophenone*.—The bright red solution formed by warming the preceding compound (0·5 g.) in concentrated sulphuric acid (2·5 c.c.) was cooled, diluted with glacial acetic acid (12 c.c.), and titrated with a solution (1·3 c.c.) of 30% hydrogen peroxide (1 vol.) in acetic acid (2 vol.). After 15 min. the *product* was collected and formed yellow prisms, m. p. 176°, from acetic acid (Found: C, 62·7; H, 4·0. $C_{22}H_{18}O_7N_2$ requires C, 62·6; H, 4·3%).

3 : 4 : 6-*Trimethylcatechol*.—Phenylhydrazine (0·8 c.c.) was added to a solution of the preceding compound (0·5 g.) in benzene (10 c.c.) and after 15 hr. at ordinary temperature 5 : 7-dinitro-1 : 3-diphenylindazole which had separated was filtered off. The filtrate was extracted with very dilute aqueous sodium hydroxide, the aqueous layer being run directly into a concentrated solution of ammonium sulphate acidified with dilute sulphuric acid. The *trimethylcatechol* so liberated was recovered and dried in ether, and sublimed at 20 mm., forming colourless crystals (yield 56%) of sharp m. p. 110° from light petroleum (b. p. 60—80°) (Found: C, 70·9; H, 8·1. $C_9H_{12}O_2$ requires C, 71·0; H, 7·95%). Beer, Jaquiss, Robertson, and Savige [12] who do not record analyses report m. p. 118—120°.

6-*Benzoyl*-1 : 3 : 4(or 1 : 2 : 4)-*trimethyl*-7-*nitrodibenzo*-p-*dioxin*.—By using piperidine (0·35 c.c.) in place of phenylhydrazine in the preceding experiment, the same catechol was obtained in meagre yield, and the ultimate benzene solution afforded the *dioxin* as yellow needles, m. p. 241° (Found: C, 70·7; H, 4·3; N, 4·0. $C_{22}H_{17}O_3N$ requires C, 70·4; H, 4·6; N, 3·7%). This dibenzodioxin was the sole product isolated when the (hydroxytrimethylphenoxy)dinitrobenzophenone was (*a*) heated in aqueous pyridine, (*b*) warmed with piperidine, (*c*) heated in acetone with suspended potassium carbonate, or (*d*) dissolved in ethanol and treated with dilute sodium hydroxide. Treated in concentrated sulphuric acid with a drop of dilute nitric acid it gave the blue colour characteristic of dibenzodioxins.

1-*Benzoyl*-3-*nitrodibenzo*-p-*dioxin* (II).—(*a*) A solution of 2-*o*-hydroxyphenoxy-3 : 5-dinitrobenzophenone (0·2 g.) in pyridine (5 c.c.) was treated with water to incipient turbidity and then heated at 100° for 1 hr. The *dioxin*, which separated from the cooled solution, had m. p. 146° (from ethanol) (Found: C, 68·9; H, 3·7. $C_{19}H_{11}O_5N$ requires C, 68·5; H, 3·3%). (*b*) The same compound was obtained when a solution of catechol (1 mol.) and 2-chloro-3 : 5-dinitrobenzophenone (1 mol.) in acetone was heated with potassium carbonate (1 mol.) for 30 min. before the whole was added to dilute hydrochloric acid. The same reagents at ordinary temperature afforded the benzophenone (I; R = NO_2), m. p. and mixed m. p. 160°.

1 : 3-Dinitrodibenzo-*p*-dioxin, m. p. 194° (from benzene), was obtained when a solution of catechol (1 g.) and picryl chloride (0·5 g.) in acetone (20 c.c.) was gently warmed and the whole added to water (Found: C, 52·7; H, 2·2. Calc. for $C_{12}H_6O_6N_2$: C, 52·6; H, 2·2%). Hillyer [1] records m. p. 192—192·5°.

1-*Nitrodibenzo*-p-*dioxin*, m. p. 126° (from methanol), was prepared, as in the preceding experiment, from 1-chloro-2 : 6-dinitrobenzene (Found: C, 63·1; H, 3·1. $C_{12}H_7O_4N$ requires C, 62·9; H, 3·1%).

Catechol bis-2 : 4-*dinitrophenyl ether*, m. p. 136° (from ethanol), was obtained by heating a mixture of catechol, 1-chloro-2 : 4-dinitrobenzene, and potassium carbonate (1 mol. each) until reaction was complete; it was liberated by trituration with water (Found: C, 49·1; H, 2·5. $C_{18}H_{10}O_{10}N_4$ requires C, 48·9; H, 2·3%).

Attempts to prepare catechol mono-2 : 4-dinitrophenyl ether failed to provide a pure product. However, by heating guaiacol 2 : 4-dinitrophenyl ether with hydrobromic acid in acetic acid an oily phenol was obtained and was characterised (*a*) by formation of a crystalline, bronze-coloured sodium salt (in which the metal appeared to be covalently bound), (*b*) by remethylation to the guaiacol ether, and (*c*) by scission with hot piperidine to catechol. Attempts to convert this phenol or its sodium salt into 2-nitrobenzodioxin failed, nor could elimination of nitrite ion be detected.

THE UNIVERSITY, GLASGOW, W.2. [*Received, January 28th*, 1959.]

[12] Beer, Jaquiss, Robertson, and Savige, *J.*, 1954, 3672.

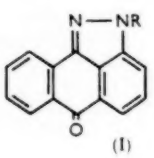
XUM

378. *Formation of Quinones by Union of Ketones. The Structure of Indanthrene Navy Blue R.*

By William Bradley and K. H. Shah.

The constitutions assigned to the products obtained by reaction of 1 : 9-pyrazoloanthrone with 3-bromo*meso*benzanthrone and subsequent cyclisation have been confirmed. The course of the reactions has been investigated and shown to be ionic in character.

B.I.O.S. Final Report No. 1493, p. 26, records the preparation of a compound (Indanthrene Navy Blue R) by the condensation of 1 : 9-pyrazoloanthrone (I; R = H) with 3-bromo*meso*benzanthrone (II; X = Br) and treatment of the product with ethanolic potassium hydroxide. The blue dye was assigned[1] structure (IV) on the grounds of



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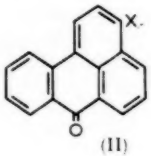

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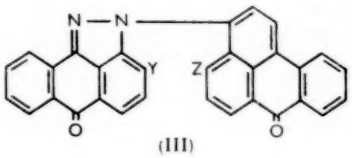
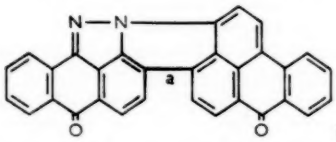


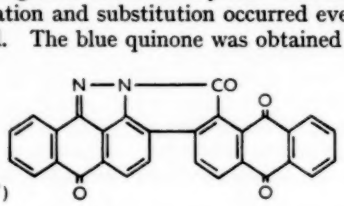
(III)



(IV)

composition and behaviour as a quinone, being reduced with alkaline sodium dithionite to an alkali-soluble product. This gave back the original compound on being oxidised in air. The purpose of the present work was to confirm structure (IV) and to study the reactions by which the dye had been formed.

It was found that the condensation of 1 : 9-pyrazoloanthrone with 3-bromo*meso*benzanthrone was much improved when the first was used as the potassium salt (I; R = K) and the reaction carried out in nitrobenzene. Purification gave 1′-(*meso*benzanthron-3-yl)pyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (III; Y = Z = H), the structure of which follows from reactions to be described. For conversion of the compound (III; Y = Z = H) into the blue quinone, sodium hydroxide in pentyl alcohol at 110—120° was found to give the maximum yield. Sodium anilide was more active, but with this reagent degradation and substitution occurred even at 10°; at 60° side reactions were still more marked. The blue quinone was obtained crystalline and with the expected composition,



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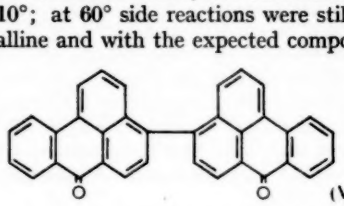


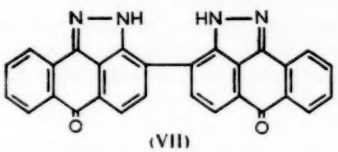
(VI)

$C_{21}H_{14}O_2N_2$. Reductive acetylation gave a magenta diacetyl derivative of a dihydro-compound, $C_{35}H_{20}O_4N_2$. On being oxidised with chromium trioxide in aqueous sulphuric acid the blue quinone gave a green lactam, $C_{29}H_{12}O_4N_2$ (V), which also behaved as a quinone towards alkaline sodium dithionite.

The main uncertainty in the structure of the blue quinone (IV) was of the bond (a) and to elucidate this point the union of *meso*benzanthrone with 1 : 9-pyrazoloanthrone in the

[1] "Colour Index," 2nd edn., 1956, Vol. III, No. 70,500.

presence of bases was studied. With alkaline reagents *meso*benzanthrone alone gives bi(*meso*benzanthron-4-yl) (VI) and violanthrone,[2] whilst 1 : 9-pyrazoloanthrone alone affords Pyrazoloanthrone Yellow[3] (VII). All these products were found in the reaction between the compounds (I; R = H) and (II; X = H) in the presence of sodium anilide, but a small proportion of 2-(*meso*benzanthron-4-yl)-1 : 9-pyrazoloanthrone (VIII; X = H) was formed also. This diketone resembles the diketone (VII) in physical and chemical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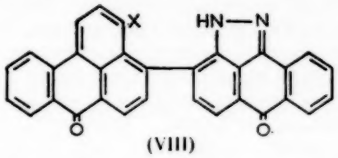
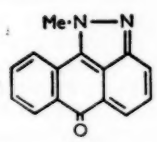
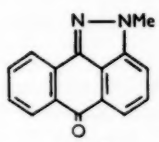
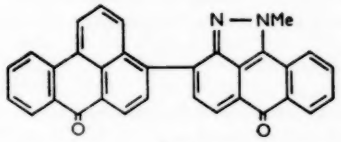

(VIII)

properties and differs considerably from (VI). It forms a red alkali-metal salt and an *N*-benzoyl derivative, and readily yields a turquoise-blue reduction product with alkaline sodium dithionite. In contrast, the compound (VI) shows no quinonoid properties. With bromine in chlorosulphonic acid containing iodine the compound (VIII) gave a monobromo-derivative, considered to be 2-(3-bromo*meso*benzanthron-4-yl)-1 : 9-pyrazoloanthrone (VIII; X = Br) for the reason that *meso*benzanthrone is most easily brominated in the 3-position [1] and because of the following reaction. Heating the bromo-derivative in nitrobenzene with anhydrous potassium carbonate gave a blue quinone identical with that of B.I.O.S. 1493, p. 26. It follows that the quinone possesses structure (IV) and that the intermediate product obtained by reaction of 1 : 9-pyrazoloanthrone with 3-bromo-*meso*benzanthrone is represented correctly by (III; Y = Z = H).

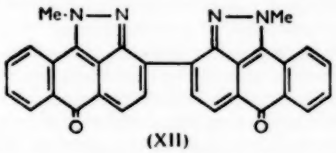
1 : 9-Pyrazoloanthrone forms two isomeric *N*-methyl derivatives of which (IX) is much more reactive towards nucleophilic substituting agents than is (X). In addition the isomer (IX) undergoes self-union in the presence of bases more readily than does (X).[4] Analogously, the latter was not observed to condense with *meso*benzanthrone in the


(IX)


(X)


(XI)

presence of sodium anilide whilst the former condensed more readily than 1 : 9-pyrazoloanthrone itself, the product consisting of 2-(*meso*benzanthron-4-yl)-1′-methylpyrazolo-(3′ : 4′ : 5′-1 : 13 : 9)anthrone (XI) and other derivatives. With equimolar amounts of reactants the yield of compound (XI) was of the same order as that of the symmetrical derivative (XII) which is formed so readily when the derivative (IX) is used alone. The result indicates that the product (XI) cannot be formed by a radical type reaction, which should favour the symmetrical compound (XII). If on the contrary the coupling reaction


(XII)

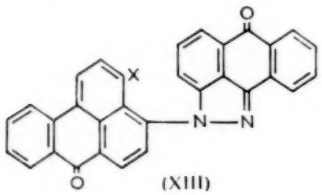
is ionic it remains to be decided whether *meso*benzanthrone or the pyrazoloanthrone (IX)

[2] Lüttringhaus and Neresheimer, *Annalen*, 1929, **473**, 259.
[3] Mayer and Heil, *Chem.-Ztg., Fortschrittsber.*, 1929, p. 56.
[4] Bradley and Bruce, *J.*, 1954, 1894.

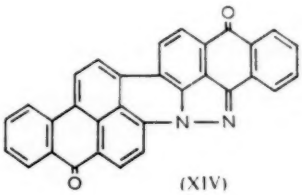
initiates the reaction. *N*-Methyl-1 : 9-pyrazoloanthrone (IX) undergoes self-union more rapidly than *meso*benzanthrone in the presence of bases, and for this reason it is probable that the formation of (VIII; X = H) is initiated by ionisation of (IX), the anion of which then attacks a molecule of *meso*benzanthrone.

A decision as to the course of the cyclisation (III; Y = Z = H) ⟶ (IV) is less easy because compound (III; Y = Z = H) belongs to the same chemical class as (X) which undergoes self-union only with difficulty. Indeed it appears more probable that with compound (III) cyclisation begins with the ionisation of the *meso*benzanthrone portion.

An attempt to prepare the diketone (VIII; X = H) by Ullmann condensation of 4-chloro*meso*benzanthrone and 2-chloro-1 : 9-pyrazoloanthrone was unsuccessful, as also were several attempts to prepare its derivatives.



(XIII)



(XIV)

Reaction of 4-chloro*meso*benzanthrone with the potassium derivative (I; R = K) gave 1′-(*meso*benzanthron-4-yl)pyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone (XIII; X = H) (XIII) (cf. U.S.P. 1,873,925) which did not cyclise to a quinone with sodium hydroxide in pentyl alcohol or sodium anilide. Bromination of 4-chloro*meso*benzanthrone gave a mono(3?)-bromo-derivative, which with the potassium derivative (I; R = K) afforded a bromo-derivative (XIII; X = Br?), the 4-chloro-substituent being eliminated. Further treatment with sodium anilide gave a crystalline reddish-brown quinone but this was not obtained free from bromine. Nitration of 4-chloro*meso*benzanthrone gave the 3-nitro-derivative [5] and this gave the derivative (XIII; X = NO_2) from which the nonacyclic product (XIV) resulted on treatment with alcoholic potassium hydroxide.

Experimental

1′-(meso*Benzanthron*-3-*yl*)*pyrazolo*(5′ : 4′ : 3′-1 : 13 : 9)*anthrone* (III; Y = Z = H).—A solution of potassium hydroxide (1 g.) in methanol (5 ml.) was added to one of 1 : 9-pyrazoloanthrone (4·4 g.) in hot pyridine (40 ml.). After 30 min. benzene was added and the potassium salt which separated was collected and dried (4·4 g.). A mixture of the potassium salt (10 g.), 3-bromo*meso*benzanthrone (10 g.), and nitrobenzene (150 ml.) was stirred for 24 hr. under reflux. The suspension which was formed was filtered and the residue washed with alcohol, extracted with boiling water, and then dried (12 g.). Crystallisation from nitrobenzene gave yellow *needles* which dissolved in concentrated sulphuric acid to form a non-fluorescent orange-red solution (Found: C, 82·7; H, 3·6; N, 6·5. $C_{31}H_{16}O_2N_2$ requires C, 83·0; H, 3·6; N, 6·3%). The procedure is an improvement on that described,[6] which also does not record an analysis of the product.

5 : 10-*Dihydro*-5 : 10-*dioxoanthra*[9,1,2-jkl]*benz*[6,7]*indazolo*[4,3,2-cde]*acridine* (IV) (cf. Ring Index No. 3919).—The yellow needles (10 g.) obtained in the preceding preparation were stirred for 5 hr. at 110° with sodium hydroxide (30 g.) and pentyl alcohol (120 ml.). The resulting suspension was distilled in steam, then acidified, and the solid was collected, dried (10 g.), and extracted (Soxhlet) with acetone, then pyridine. The residue was extracted with alkaline sodium dithionite, and the blue solution which was formed was filtered and aerated. A precipitate formed, was collected, was hed, dried, and crystallised from nitrobenzene. It gave blue needles (Found: C, 82·9; H, 3·2; N, 6·2. Calc. for $C_{31}H_{14}O_2N_2$: C, 83·4; H, 3·1; N, 6·3%) which dissolved in concentrated sulphuric acid with a blue colour.

[5] G.P. 450,445, 492,248.
[6] B.I.O.S. Final Report, No. 1493, p. 26.

The same quinone (IV) was obtained when the product (III; Y = Z = H) was stirred for 2 hr. at 0—5° with a solution of sodium anilide in aniline.

5 : 10-*Diacetoxyanthra*[9,1,2-jkl]*benz*[6,7]*indazolo*[4,3,2-cde]*acridine*.—Zinc dust (5 g.) was added gradually to a suspension of the quinone (IV) (1 g.) in acetic anhydride (20 ml.) which was stirred under reflux. After the addition was complete refluxing was continued for 5 hr. and then the suspension was filtered, the filtrate was added to dilute hydrochloric acid, the precipitate was collected, dried, and extracted with pyridine, and the solution so obtained added to water. The precipitate was collected, washed with acetone, and dried (Found: C, 78·4; H, 4·0; N, 5·7. $C_{35}H_{20}O_4N_2$ requires C, 78·9; H, 3·8; N, 5·3%). This *diacetoxy-derivative* dissolved readily in pyridine forming a magenta solution.

Oxidation of Quinone (IV) *to the Lactam* (V).—A solution of the quinone (IV) (5·5 g.) in concentrated sulphuric acid (150 ml.) was added slowly to a boiling solution of chromium trioxide (22·5 g.) in water (695 ml.) through which air was passed. After 4 hr. a further portion of chromium trioxide (7·5 g.) was added and refluxing continued for 12 hr. Water was then added and the precipitate formed was collected and dissolved in alkaline sodium dithionite. The red-violet solution which resulted was filtered and the filtrate aerated. The solid which separated was collected, heated in concentrated sulphuric acid for 1 hr., and recovered by addition to water. After being dried it crystallised from nitrobenzene as green needles (Found: C, 76·9; H, 2·7; N, 6·1. $C_{29}H_{12}O_4N_2$ requires C, 77·0; H, 2·7; N, 6·2%). This *lactam* of 2-(2′-anthraquinonyl)-1 : 9-pyrazoloanthrone-1′-carboxylic acid dissolves in alkaline sodium dithionite forming a reddish-brown solution.

N-*Benzoyl*-2-(meso*benzanthron*-4-*yl*)-1 : 9-*pyrazoloanthrone* (N-*Benzoyl Derivative of* VIII; X = H).—1 : 9-Pyrazoloanthrone (10 g.), *meso*benzanthrone (10 g.), and glucose (10 g.) were refluxed with stirring for 7 hr. in alcohol (150 g.) containing potassium hydroxide (100 g.). Water was then added, air was passed through the resulting suspension, and finally this was acidified. The solid formed (23 g.) was collected, washed, dried, and extracted with acetone and then with hot trichlorobenzene. The latter extract was chromatographed on alumina, and the bands were developed with trichlorobenzene. The column was washed with alcohol and dried, and the adsorbate eluted from the main band with pyridine (Soxhlet). The pyridine solution so obtained was added to dilute hydrochloric acid, and the precipitate (1·4 g.) was collected, dried, and heated with benzoyl chloride for 4 hr. The *N*-benzoyl derivative was then isolated by the addition of ether, filtration, and warming of the filtrate with aqueous sodium carbonate. A solid was formed and this was taken up in chlorobenzene and chromatographed on alumina. The principal band was yellow; it was eluted with pyridine, and the solute separated by addition of the extract to dilute hydrochloric acid. N-*Benzoyl*-(2-meso*benzanthron*-4-*yl*)-1 : 9-*pyrazoloanthrone* crystallised from aniline–tetralin in yellow plates (Found: C, 82·6; H, 3·6; N, 5·0. $C_{36}H_{20}O_3N_2$ requires C, 82·6; H, 3·6; N, 5·1%).

2-(meso*Benzanthron*-4-*yl*)-1 : 9-*pyrazoloanthrone* (VIII; X = H).—(*a*) On being refluxed for 12 hr. with potassium hydroxide in *tert.*-butyl alcohol the foregoing *N*-benzoyl derivative gave 2-(meso*benzanthron*-4-*yl*)-1 : 9-*pyrazoloanthrone* which crystallised from nitrobenzene in greenish-yellow plates (Found: C, 83·2; H, 3·7; N, 6·2. $C_{31}H_{16}O_2N_2$ requires C, 83·0; H, 3·6; N, 6·3%). It formed a red potassium salt and dissolved in alkaline sodium dithionite with a turquoise-blue colour. (*b*) 2-(*meso*Benzanthron-4-yl)-1 : 9-pyrazoloanthrone was prepared directly by the interaction of *meso*benzanthrone and 1 : 9-pyrazoloanthrone under the following conditions. *meso*Benzanthrone (10 g.), 1 : 9-pyrazoloanthrone (10 g.), and aniline (60 g.) were added at 40—45° to a stirred solution of sodium anilide prepared by refluxing sodium (5 g.), copper bronze (0·2 g.), and nickel oxide (0·2 g.) with " AnalaR " aniline (150 ml.) under nitrogen. After 2 hr. the resulting suspension was cooled and added to dilute hydrochloric acid containing ice, and the solid (22 g.) formed was collected, washed, and dried. It was then extracted (Soxhlet) with acetone, and the insoluble part (11 g.) was extracted with hot trichlorobenzene. The residue (5 g.) consisted mainly of bi-(1 : 9-pyrazoloanthron-2-yl). The extract was chromatographed on alumina at 160—170° and the bands were developed further with trichlorobenzene. A red substance passed through the column followed by bi-(*meso*benzanthron-4-yl) as a greenish-yellow band. After washing of the column with alcohol the material which remained was eluted with pyridine and separated by addition of the eluate to dilute hydrochloric acid. The precipitate so formed was collected, washed, and extracted with alkaline sodium dithionite. On being aerated the extract afforded a precipitate which after being extracted with acetone was dissolved in nitrobenzene and chromatographed on alumina at 140°.

XUM

A main band consisting of 2-(*meso*benzanthron-4-yl)-1 : 9-pyrazoloanthrone was formed. Violanthrone also was formed in the sodium anilide reaction, the amount increasing with the temperature at which the condensation was carried out.

Two other experiments were carried out, with sodium anilide at 40—45° in which the proportions of the reactants were varied. The results obtained were:

*meso*Benzanthrone (g.)	1 : 9-Pyrazoloanthrone (g.)	Na (g.)	Yield (g.) of (VIII; X = H)
34·5	6·6	10	0·02
6·9	33·0	10	0·03

It was not possible to prepare compound (VIII; X = H) by heating a mixture of 2-chloro-1 : 9-pyrazoloanthrone and 4-chloro*meso*benzanthrone, or by the action of sodium anilide on a mixture of 1 : 9-pyrazoloanthrone and 4-chloro*meso*benzanthrone at 45—50° (3 hr.). None was formed when *meso*benzanthrone-4-carboxylic acid [7] (3 g.) was heated with 1 : 9-pyrazoloanthrone (12·5 g.) at 300—320° for 5 hr.

Reaction of meso*Benzanthrone with* 1′-*Methylpyrazolo*(3′ : 4′ : 5′-1 : 13 : 9)*anthrone.*—*meso*-Benzanthrone (4·5 g.) and 1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthrone (4·5 g.) were stirred for 2 hr. at 45—50° with sodium anilide prepared from sodium (2·4 g.) and aniline (75 ml.). The product was worked up as in (*b*) (above) and finally purified by dissolution in alkaline sodium dithionite solution, filtration, and reprecipitation by aeration of the filtrate. The solid (3 g.) so obtained was extracted with acetone, and the residue (2 g.) taken up in nitrobenzene and chromatographed on alumina at 100—120°; a small orange-red fraction consisting of bi-[1′-methylpyrazolo(3′ : 4′ : 5′-1 : 13 : 9)anthron-2-yl] remained undissolved.[4] The main band was eluted with nitrobenzene, and the solute recovered by concentration of the extract. 2-(meso*Benzanthron-4-yl*)-1′-*methylpyrazolo*(3′ : 4′ : 5′-1 : 13 : 9)*anthrone* (XI) crystallised from nitrobenzene as orange needles (Found: C, 82·7; H, 4·0; N, 6·3. $C_{32}H_{18}O_2N_2$ requires C, 83·1; H, 3·9; N, 6·1%), which dissolved in concentrated sulphuric acid with an orange-red colour and in alkaline sodium dithionite forming a blue solution.

When the isomeric 1′-methylpyrazolo(5′ : 4′ : 3′-1 : 13 : 9)anthrone was used in the preceding experiment no union with *meso*benzanthrone was observed.

2-(3-*Bromo*meso*benzanthron-4-yl*)-1 : 9-*pyrazoloanthrone* (VIII; X = Br).—A solution of 2-(*meso*benzanthron-4-yl)-1 : 9-pyrazoloanthrone (0·4 g.) in chlorosulphonic acid (7 ml.) was stirred with bromine (0·2 ml.) and a trace of iodine for 24 h. at the room temperature. Sulphuric acid was then added and the whole added to water. The product which separated was stirred with sodium metabisulphite solution, collected, and washed with water. It was a green solid which was not obtained pure (Found: Br, 19. Calc. for $C_{31}H_{15}O_2N_2Br$: Br, 15%). It dissolved in alkaline sodium dithionite forming a green solution.

Cyclisation. A solution of the bromo-derivative (0·3 g.) in nitrobenzene (10 ml.) containing anhydrous potassium carbonate (0·3 g.) was refluxed for 12 hr. On being cooled, this gave a greenish-blue precipitate. This was collected and extracted with nitrobenzene, and the solution so obtained was chromatographed on alumina at 160—170°. A blue band formed. This was eluted with nitrobenzene, the eluate steam-distilled, and the residue chromatographed in alkaline sodium dithionite and on cellulose powder with alcoholic alkaline sodium dithionite to develop the bands. A small green fraction passed through the column first, followed by a large blue band. The latter was collected, and the colouring matter was precipitated by aeration and crystallised from nitrobenzene (Found: N, 6·0. Calc. for $C_{31}H_{14}O_2N_2$: N, 6·3%). It was identical with the quinone (IV) formed by cyclisation of (III; X = Y = H); like this it showed no reaction when a drop of 30% methanolic potassium hydroxide was added to its blue solution in dry pyridine.

N-(meso*Benzanthron-4-yl*)-1 : 9-*pyrazoloanthrone.*—The potassium salt of 1 : 9-pyrazoloanthrone (1 g.) and 4-chloro*meso*benzanthrone (1 g.) were refluxed for 24 hr. with stirring in dry nitrobenzene (10 ml.). The precipitate formed was collected, washed with alcohol, extracted with hot water, and then dried. N-meso*Benzanthron-4-yl*-1 : 9-*pyrazoloanthrone* crystallised from nitrobenzene in greenish-yellow needles (Found: C, 83·0; H, 3·7; N, 6·4. $C_{31}H_{16}O_2N_2$ requires C, 83·0; H, 3·6; N, 6·2%). It dissolved in concentrated sulphuric acid with a red colour. This derivative did not cyclise to a quinonoid compound when 1 g. was heated with sodium hydroxide (3 g.) and pentyl alcohol (12 ml.) at 110° for 24 hr. with stirring. Similarly no cyclisation was observed with sodium anilide in aniline at 80°.

[7] Bradley and Shah, following paper.

Bromination of 4-*Chloro*mesobenzanthrone.—(*a*) A solution of bromine (1 ml.) in nitrobenzene (5 ml.) was added dropwise during 2 hr. to a suspension of 4-chloro*meso*benzanthrone (4·4 g.) in nitrobenzene (20 ml.) containing iodine (0·01 g.) which was stirred at 100°. The reaction was continued for 16 hr. and then the suspension was cooled. Benzene was added, and the precipitate was collected, washed with alcohol, and crystallised from xylene (norite). 3-*Bromo*-4-*chloro*mesobenzanthrone forms yellow needles, m. p. 220° (Found: C, 57·5; H, 2·6. $C_{17}H_8OClBr$ requires C, 59·4; H, 2·3%. 5·699 mg. gave 5·527 mg. of mixed silver halides; calc. for $C_{17}H_8OClBr$, 5·499 mg.). (*b*) In a similar experiment in which the reactants were bromine (0·6 ml.), iodine (0·05 g.), and 4-chloro*meso*benzanthrone (1 g.) stirred in nitrobenzene (15 ml.) at 130° for 4 hr. the product was chromatographed on alumina at 60° from a solution in chlorobenzene. The main fraction crystallised from chlorobenzene as yellow, flat needles, m. p. 259—260° (Found: C, 47·9; H, 1·7. $C_{17}H_7OClBr_2$ requires C, 47·2; H, 1·7%. 6·443 mg. gave 7·405 mg. of mixed silver halides. Calc. for $C_{17}H_7OClBr_2$: 7·884 mg.).

N-(3-*Bromo*mesobenzanthron-4-*yl*)-1 : 9-*pyrazoloanthrone*.—Potassium 1 : 9-pyrazoloanthrone (1·3 g.) and 3-bromo-4-chloro*meso*benzanthrone [1·7 g.; prepared as in (*a*) above] were refluxed together in nitrobenzene (25 ml.) for 24 hr. The resulting suspension was cooled, and the solidwas collected (1·5 g.) and crystallised from nitrobenzene. N-(3-*Bromo*mesobenzanthron-4-*yl*-1 : 9-*pyrazoloanthrone* formed greenish-yellow needles (Found: C, 70·8; H, 3·0; N, 5·2; Br, 15·3. $C_{31}H_{15}O_2N_2Br$ requires C, 70·6; H, 2·8; N, 5·3; Br, 15·2%) which dissolved in concentrated sulphuric acid with a red colour.

N-(3-*Nitro*mesobenzanthron-4-*yl*)-1 : 9-*pyrazoloanthrone*.—4-Chloro-3-nitro*meso*benzanthrone [5] (5 g.) and potassium 1 : 9-pyrazoloanthrone (5 g.) were refluxed in nitrobenzene (50 ml.) for 24 hr. The product was isolated as for the 3-bromo-derivative and crystallised from nitrobenzene. N-(3-*Nitro*mesobenzanthron-4-*yl*)-1 : 9-*pyrazoloanthrone* forms orange-yellow plates (Found: N, 8·8. $C_{31}H_{15}O_4N_3$ requires N, 8·5%).

Conversion into the Quinone (XIV).—The 3-nitro-derivative (5 g.) was stirred for 7 hr. with potassium hydroxide (30 g.) in ethanol (50 g.). Water was then added and the resulting suspension aerated. The solid formed was collected and dissolved in alkaline sodium dithionite, and the solution so obtained was filtered and again aerated. The precipitate was crystallised from nitrobenzene and the *quinone* (XIV) was obtained as reddish-brown needles (Found: C, 83·2; H, 3·1; N, 6·0. $C_{31}H_{14}O_2N_2$ requires C, 83·4; H, 3·1; N, 6·3%) which dissolved with a blue colour both in concentrated sulphuric acid and in alkaline sodium dithionite solution.

2-*Chloro*-1 : 9-*pyrazoloanthrone*.—99—100% Hydrazine hydrate (4·5 ml.) was added dropwise to a refluxing solution of 1 : 2-dichloroanthraquinone (13·5 g.) in pyridine (150 ml.). Heating was then continued for 6 hr. The solution formed was cooled and added to water, and the 2-*chloro*-1 : 9-*pyrazoloanthrone* so obtained was crystallised from chlorobenzene (norite) as pale greenish-yellow needles, m. p. 286° (Found: C, 66·2; H, 2·8; N, 11·0; Cl, 14·0. $C_{14}H_7ON_2Cl$ requires C, 66·1; H, 2·7; N, 11·0; Cl, 13·9%). The red potassium salt separated when potassium hydroxide (0·5 g.) in methanol (5 ml.) was added to a solution of the derivative (2·5 g.) in pyridine (40 ml.). Attempts to bring the salt into reaction with 3-bromo*meso*benzanthrone and 4-chloro*meso*benzanthrone were unsuccessful.

2-*Amino*-1 : 9-*pyrazoloanthrone*.—Reaction of 2-amino-1-chloroanthraquinone (5 g.) with 99—100% hydrazine hydrate (2·5 ml.) in pyridine (50 ml.) under reflux for 12 hr. gave 2-*amino*-1 : 9-*pyrazoloanthrone* (3·5 g.), which crystallised from nitrobenzene as brown needles with a green fluorescence (Found: C, 71·3; H, 4·0; N, 17·4. $C_{14}H_9ON_3$ requires C, 71·5; H, 3·9; N, 17·9%). It formed a potassium salt, but an attempt to bring this into reaction with 3-bromo-*meso*benzanthrone was unsuccessful.

3-*Nitro*mesobenzanthrone-4-*carboxylic Acid*.—A solution of nitric acid (*d* 1·5; 1 ml.) in nitrobenzene (5 ml.) was added during 1 hr. to a suspension of *meso*benzanthrone-4-carboxylic acid (2 g.) in nitrobenzene (20 ml.) heated on a boiling-water bath. Heating was continued for 1 hr. longer, then the resulting solution was cooled. Benzene was then added and the solid which was precipitated was collected [1·7 g.; m. p. 310° (decomp.)] and purified by dissolution in aqueous sodium hydroxide and reprecipitation from the filtered solution. 3-*Nitro*mesobenzanthrone-4-*carboxylic acid* crystallised from nitrobenzene as yellow plates (Found: C, 67·7; H, 3·1; N, 4·4. $C_{18}H_9O_5N$ requires C, 67·7; H, 2·8; N, 4·4%).

Methyl ester. By the Schotten–Baumann method the acid gave the *methyl ester* as golden-yellow plates (from dioxan), m. p. 245° (Found: C, 68·7; H, 3·5; N, 4·0. $C_{19}H_{11}O_5N$ requires C, 68·5; H, 3·3; N, 4·2%).

XUM

No condensation product could be isolated from the acid or the methyl ester with α-aminoanthraquinone or the potassium salt of 1 : 9-pyrazoloanthrone.

Reduction. 3-Nitro*meso*benzanthrone-4-carboxylic acid (5 g.), sodium sulphide crystals (5 g.), water (20 ml.), and methanol (80 ml.) were stirred under reflux for 4 hr. The resulting solution was filtered, the filtrate was acidified, and the precipitate purified from nitrobenzene as brown crystals, m. p. 278°, which appeared to be identical with the lactam, m. p. 278°, of 3-amino*meso*benzanthrone-4-carboxylic acid obtained [8] by the action of acids on 4-methyl-3-nitro*meso*benzanthrone.

3-*Bromo*meso*benzanthrone-4-carboxylic Acid.*—*meso*Benzanthrone-4-carboxylic acid (1·5 g.) was stirred at 40° for 3 hr. with a solution of bromine (0·3 ml.) and a trace of iodine in chlorosulphonic acid (5 ml.). Sulphuric acid was then added and the resulting solution poured into water. The precipitate which formed was collected, washed, and then dissolved in dilute sodium hydroxide. Acidification of the filtered solution gave 3-bromo*meso*benzanthrone-4-carboxylic acid which crystallised from dioxan as greenish-yellow needles, m. p. 305° (Found: C, 59·5; H, 3·0; Br, 22·1. $C_{18}H_9O_3Br,0{\cdot}5H_2O$ requires C, 59·6; H, 2·8; Br, 22·1%), which did not react when heated with the potassium salt of 1 : 9-pyrazoloanthrone.

Ethyl 1 : 9-*Pyrazoloanthrone-2-carboxylate.*—1 : 9-Pyrazoloanthrone-2-carboxylic acid (5 g.; prepared from 1-chloroanthraquinone-2-carboxylic acid according to G.P. 515,680) was refluxed for 2 hr. with thionyl chloride (15 ml.) in trichlorobenzene (50 ml.). On being cooled the *chloride* crystallised and this was collected, added to dry ethanol, and refluxed for 2 hr. The resulting solution was cooled and the *ethyl* 1 : 9-*pyrazoloanthrone-2-carboxylate* which separated crystallised from dioxan as yellow needles, m. p. 220° (Found: C, 69·6; H, 4·4; N, 9·9. $C_{17}H_{12}O_3N_2$ requires C, 69·8; H, 4·1; N, 9·6%).

Potassium 1 : 9-pyrazoloanthrone-2-carboxylate did not react with 3-bromo*meso*benzanthrone in refluxing nitrobenzene during 24 hr.

We thank the British Council for the award of a Colombo Plan Fellowship (to K. H. S.).

CLOTHWORKERS RESEARCH LABORATORY,
UNIVERSITY OF LEEDS. [*Received, January 12th,* 1959.]

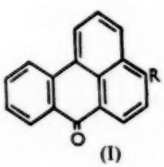
[8] G.P. 482,560.

NOTES.

379. *Catalytic Action of Quinones in the Oxidation of* 4-*Methyl*meso*benzanthrone to* meso*Benzanthrone*-4-*carboxylic Acid.*

By WILLIAM BRADLEY and K. H. SHAH.

THE catalytic effect of quinones on oxidation is well known [1] and the present is a further example in which the oxidant is nitrobenzene and barium hydroxide. In attempts to prepare *meso*benzanthrone-4-carboxylic acid (I; R = CO_2H) from 4-methyl*meso*benzanthrone (I; R = Me) by using an alkali and nitrobenzene with a trace of a copper salt the reaction was capricious and the yields were low. The addition of various quinones improved both the yield and the smoothness, 1 : 2-benzanthraquinone being the most effective of the quinones tried The Table shows the yields of *meso*benzanthrone-4-carboxylic acid prepared under the following conditions.[2] 4-Methyl*meso*benzanthrone (10 g.) and the selected quinone (0·5 g.) were stirred in nitrobenzene (100 ml.) at 160—180° for 2 hr. whilst barium hydroxide octahydrate (25 g.) and a trace of copper sulphate were added portionwise.



(I)

[1] Perkin and Spencer, *J.*, 1922, 479.
[2] B.P. 277,670; G.P. 576,176, 479,917; Copp and Simonsen, *J.*, 1942, 209.

Heating was continued for 1 hr. longer and then the alkali-soluble part of the product was separated.

Quinone	Yield of *meso*benzanthrone-4-carboxylic acid (g.)
None	1·0 or less
Anthraquinone	4·0
1 : 4 : 5 : 8-Tetrachloroanthraquinone	4·2
1 : 2-Benzanthraquinone	7·0
Anthanthrone	4·5
1′ : 2′-6′ : 7′-Dibenzopyrene-7 : 14-quinone	4·5
Flavanthrone	0·25

The relative amounts of 4-methyl*meso*benzanthrone, the quinones and nitrobenzene employed, and the yields of *meso*benzanthrone-4-carboxylic acid obtained indicate that nitrobenzene is the ultimate oxidant and that the quinones act as catalysts, presumably by functioning as hydrogen-acceptors. However, a high oxidation–reduction potential is not sufficient in itself. Flavanthrone which is very easily reduced is ineffective, probably on account of its very low solubility. No oxidation was observed when nitrobenzene was replaced by anisole.

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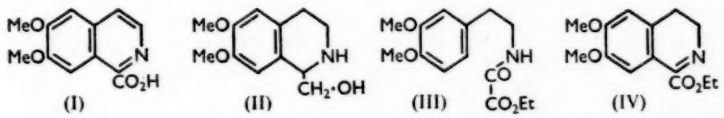
380. *The Synthesis of Calycotomine.*

By A. R. Battersby and T. P. Edwards.

The alkaloid calycotomine, $C_{12}H_{17}O_3N$, has been isolated [1] in the optically active and the (±)-form from *Calycotome spinosa* and *Cytisus proliferus*. Its properties and the oxidation of the alkaloid to 6 : 7-dimethoxy*iso*quinoline-1-carboxylic acid (I) leave little doubt [2] that it has the structure (II).



A considerable quantity of calycotomine was required in connection with other work, and we describe here the synthesis of the alkaloid. This has not previously been accomplished though earlier attempts have been made.[2]

Ethoxalyl chloride with 3 : 4-dimethoxyphenethylamine gave the amide (III) together with the bisamide of oxalic acid. When the former was cyclised over phosphoric oxide in boiling toluene, it yielded, rather slowly, the 3 : 4-dihydro*iso*quinoline (IV). Both reducible groups in this base were attacked by lithium aluminium hydride in boiling tetrahydrofuran, and the product (II) was identical with natural (±)-calycotomine. The structure of the alkaloid is thus confirmed.

Experimental.—Ethyl N-3 : 4-*dimethoxyphenethyloxamate* (III). A solution of 3 : 4-dimethoxyphenethylamine (100 g.) in dry ether (500 ml.) was added slowly to a stirred solution of ethoxalyl chloride [3] (38 g.) in dry ether (750 ml.), and stirring was continued for 1 hr. after the addition was complete. Water (500 ml.) was then added and the solution was filtered to

[1] White, *New Zealand J. Sci. Tech.*, 1944, **25**, *B*, 152.
[2] *Idem, ibid.*, 1951, **33**, *B*, 38.
[3] Adickes, Brunnert, and Lucker, *J. praht. Chem.*, 1931, **130**, 168.

remove the crude di-(3 : 4-dimethoxyphenethylamide) of oxalic acid, m. p. 165—171° (lit.,[4] m. p. 173—174°). The ethereal layer from the filtrate was washed with an excess of dilute hydrochloric acid, the washings were combined with the main aqueous solution, and this solution was then extracted thrice with ethyl acetate. Evaporation of the combined solutions in ether and ethyl acetate left a gum (74 g.) which crystallised from ether to give *ethyl* N-3 : 4-*dimethoxyphenethyloxamate* (54 g.), m. p. 71—72°. A portion was distilled at 150° (bath)/0·1 mm. for analysis (Found: C, 59·7; H, 4·9; N, 6·8. $C_{14}H_{19}O_5N$ requires C, 59·8; H, 4·9; N, 6·7%).

Ethyl 3 : 4-*dihydro*-6 : 7-*dimethoxy*isoquinoline-1-*carboxylate* (IV). " Celite " (50 g.), previously dried at 100°, was added to a solution of the foregoing amide (24 g.) in anhydrous toluene (300 ml.), and the mixture was heated under reflux. Phosphoric oxide (50 g.) was then added, followed by a further portion (25 g.) after 10 min. The mixture was then heated for 35 min., being stirred several times. After being cooled, the excess of phosphoric oxide was decomposed by water, and the " Celite " was filtered off and washed with dilute hydrochloric acid and hot benzene. The organic layer of the filtrate was shaken with dilute hydrochloric acid, and these washings were combined with the main aqueous layer. After the aqueous solution had been extracted with ether, it was adjusted to pH 9 with potassium carbonate and extracted thrice again with ether. Evaporation of the latter dried ethereal solution left the *dihydro*isoquinoline (IV) as a gum (6 g.) which crystallised from ether as needles, m. p. 79—80°.

Unchanged starting material (12 g.) was recovered by evaporation of the combined solution in toluene, benzene, and ether above and was cyclised as before, to give again a basic and a neutral fraction. The process was repeated on the latter fraction and the combined yield of dihydro*iso*quinoline (IV) was 10·8 g. (48%) (Found: C, 64·1; H, 6·7; N, 4·8. $C_{14}H_{17}O_4N$ requires C, 63·9; H, 6·5; N, 5·3%).

(±)-1 : 2 : 3 : 4-*Tetrahydro*-1-*hydroxymethyl*-6 : 7-*dimethoxy*isoquinoline (II). A solution of the above dihydro*iso*quinoline (1·04 g.) in anhydrous tetrahydrofuran (50 ml.) was added dropwise to a stirred, boiling solution of lithium aluminium hydride (0·45 g., 3 mol.) in tetrahydrofuran (50 ml.). The mixture was heated under reflux for 1 hr. After the addition of the minimum amount of water to decompose the excess of hydride, the solution was filtered, the collected solid was washed thoroughly with boiling chloroform, and the washings were added to the main solution. This was evaporated under reduced pressure to leave a solid (0·9 g.) which was dried over phosphoric oxide *in vacuo*, then boiled thrice with benzene (total 100 ml.). The extracts were concentrated to 25 ml., the tetrahydro*iso*quinoline (II) crystallising (0·46 g., 53%); it had m. p. 132—134° raised to 133·5—134·5° by further recrystallisation (Found: C, 64·3; H, 7·7; N, 6·2. Calc. for $C_{12}H_{17}O_3N$: C, 64·6; H, 7·6; N, 6·3%). The m. p. was unchanged on admixture with natural (±)-calycotomine, m. p. 133—134°, in the same bath. The infrared spectra of the synthetic and the natural base (in Nujol) were identical.

A portion of the synthetic base was converted into the hydrochloride which crystallised from ethanol and had m. p. 193—195° alone or in admixture with the hydrochloride of natural (±)-calycotomine of m. p. 194—196° in the same bath. The two samples of hydrochloride had identical infrared spectra (in Nujol).

Grateful acknowledgment is made to Dr. E. P. White, Hamilton, New Zealand, for generous gifts of calycotomine derivatives and to the University of Bristol and the Ministry of Education for grants to T. P. E.

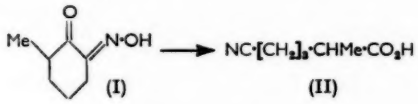
THE UNIVERSITY, BRISTOL. [*Received, January* 19*th*, 1959.]

[4] Child and Pyman, *J.*, 1929, 2010.

381. *The Second-order Beckmann Rearrangement of 2-Hydroxyimino-6-methylcyclohexanone.*

By E. B. McCall and B. B. Millward.

Wieland *et al.*[1] made use of the second-order Beckmann rearrangement [2] of an α-diketone monoxime to open a six-membered ring in a steroid nucleus. We now record the similar cleavage of 2-hydroxyimino-6-methyl*cyclo*hexanone (I) to 5-cyano-2-methylpentanoic acid (II).



The oxime (I) was prepared by the method of Jaeger and van Dijk [3] but whereas they isolated two isomers, m. p. 167° (decomp.) and 65° respectively, we obtained one oxime, m. p. 80—82°. A satisfactory analysis for this unstable material could not be obtained but direct conversion into the cyano-acid (II) was effected in good yield by toluene-*p*-sulphonyl chloride in aqueous sodium hydroxide.

Experimental.—Ethyl 3-methyl-2-oxocyclohexanecarboxylate. This ester, b. p. 139—144°/32 mm., n_D^{20} 1·471, was prepared [4] in 44% yield from 2-methyl*cyclo*hexanone, n_D^{20} 1·449. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in orange leaflets, m. p. 87—87·5° (Found: C, 53·3; H, 5·5; N, 15·2. $C_{16}H_{20}O_8N_4$ requires C, 52·7; H, 5·5; N, 15·4%). The indazolone was formed as described for a thia-derivative of indazolone by Bennett and Scorah.[5] Recrystallisation from 95% methanol gave pale yellow prisms of 3 : 4 : 5 : 6 : 7 : 9-*hexahydro*-7-*methyl*-2-*phenylindazol*-3-*one*, m. p. 135—136° (Found: C, 73·6; H, 7·3; N, 12·1. $C_{14}H_{16}ON_2$ requires C, 73·6; H, 7·1; N, 12·3%).

Hydrolysis of the ester with 2N-sodium hydroxide solution followed by acidification regenerated 2-methyl*cyclo*hexanone, b. p. 70°/29 mm., n_D^{20} 1·449. The 2 : 4-dinitrophenylhydrazone crystallised from methanol in yellow leaflets, m. p. 139° (lit.,[6] m. p. 143°).

2-*Hydroxyimino*-6-*methyl*cyclo*hexanone* (I). The foregoing ester (36 g., 0·2 mole) was added to a stirred solution of potassium hydroxide (15 g., 0·27 mole) and sodium nitrite (13·8 g., 0·2 mole) in water (250 c.c.) under nitrogen. After 46 hr. the solution was cooled to 5° and treated dropwise with sulphuric acid (12·7 c.c. of 98% acid in 100 c.c. of water): carbon dioxide was liberated. The precipitated oxime (I) was collected, washed, and dried *in vacuo* to white prisms, m. p. 78—80° (18·2 g., 65%). Extraction of the filtrate with ether gave a crude oxime which crystallised from aqueous methanol in prisms, m. p. 80—82° (1·1 g.). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethanol in orange prisms, m. p. 188—189° (Found: C, 48·8; H, 4·8; N, 21·6. $C_{13}H_{15}O_5N_5$ requires C, 48·6; H, 4·7; N, 21·8%).

5-*Cyano*-2-*methylpentanoic acid* (II). The oxime (9·5 g., 0·067 mole) was stirred in aqueous potassium hydroxide (12·8 g. in 44 c.c. of water) under nitrogen, and benzenesulphonyl chloride (9·8 c.c., 0·068 mole) was added dropwise (20 min.) at 20°. After a further 25 min. the solution was washed with chloroform, acidified, and extracted with chloroform, to yield 5-*cyano*-2-*methylpentanoic acid* (II), b. p. 142—143°/1·5 mm., n_D^{20} 1·451 (7·3 g., 77%) (Found: C, 59·9; H, 7·9; N, 9·8. $C_7H_{11}O_2N$ requires C, 59·6; H, 7·9; N, 9·9%). The p-*toluidide* crystallised from benzene in prisms, m. p. 86° (Found: C, 73·2; H, 7·5; N, 11·9. $C_{14}H_{18}ON_2$ requires C, 73·0; H, 7·9; N, 12·2%).

Hydrolysis of the cyano-acid with hot concentrated hydrochloric acid gave ammonium chloride and 2-methyladipic acid, which was crystallised with difficulty from benzene–light

[1] Wieland, Anner, and Miescher, *Helv. Chim. Acta*, 1953, **36**, 1803.
[2] Grob and Baumann, *ibid.*, 1955, **38**, 594.
[3] Jaeger and van Dijk, *Proc. Acad. Sci. Amsterdam*, 1936, **39**, 384.
[4] *Org. Synth.*, Coll. Vol. II, 1943, p. 531.
[5] Bennett and Scorah, *J.*, 1927, 196.
[6] Lecomte and Gault, *Compt. rend.*, 1954, **238**, 2538.

petroleum (b. p. 60—80°) in prisms, m. p. 55—60° (Found: C, 52·6; H, 7·9. Calc. for $C_7H_{12}O_4$: C, 52·5; H, 7·6%). Best and Thorpe [7] found m. p. 64°.

We thank Monsanto Chemicals Limited for permission to publish this work.

NICKELL LABORATORIES, MONSANTO CHEMICALS LIMITED,
RUABON, NORTH WALES. [*Received, January 29th*, 1959.]

[7] Best and Thorpe, *J.*, 1909, **95**, 712.

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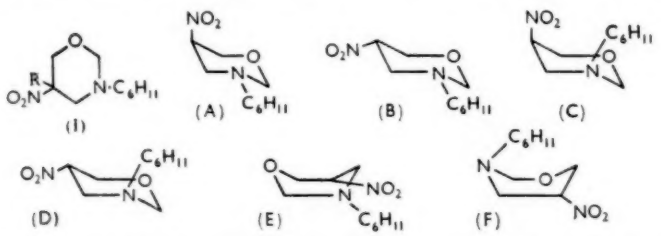
382. *The Stereochemistry of Some Tetrahydro-1 : 3-oxazine Derivatives.*

By (MRS.) D. GÜRNE and T. URBAŃSKI.

THE preparation of derivatives of tetrahydro-5-nitro-1 : 3-oxazine derivatives from primary nitro-paraffins, formaldehyde, and ammonia or primary amines has been described.[1] Their stereochemistry has now been examined. The dipole moments indicate that the ring is in the chair form with nitro- and the *cyclo*hexyl group in the axial and the equatorial conformation respectively.

We prepared the products (I; R = Me, Et, Pr^n, Pr^i, and Bu^n) from nitroethane,[2] 1-nitropropane,[3] 1-nitrobutane,[3] 1-nitro*iso*butane, and 1-nitropentane respectively by condensation with formaldehyde and treatment of the resulting 1 : 3-diols with formaldehyde and *cyclo*hexylamine. *cyclo*Hexylamine was chosen as it yields crystalline products. Dipole moments were calculated by using the group moment 3·25 D for NO_2



and the bond moments C–O 0·86 (bond length 1·43 Å) and C–N 0·45 D (bond length 1·47 Å), and the CNC and COC angles 111° and 110° 42′ respectively. Experimental values found were 4·45, 4·42, 4·41, 4·56, 4·46 D for the compounds (I; R = Me, Et, Pr^n, Pr^i, Bu^n respectively); these were referred to the chair form (A) with an axial nitro-group, for which the calculated value is 4·37 D. For form (B) with an equatorial nitro-group the calculated value is distinctly lower (μ 2·73 D). For both these calculations the *cyclo*hexyl ring is assumed to be equatorial since the axial conformations (C and D) give lower values (3·74 and 2·56 D respectively).

Boat forms give calculated dipole moments ranging from 2·17 (lowest) (conformation E) to 3·74 D (highest) (conformation F).

EXPERIMENTAL

*3-cyclo**Hexyltetrahydro-5-nitro-5-iso**propyl-1 : 3-oxazine.*—2-Nitro-2-*iso*propylpropane-1 : 3-diol (prepared from 1-nitro*iso*butane and formaldehyde) (0·1 mol., 16·3 g.) was mixed with 30%

[1] Hirst, Jones, Minahan, Ochyński, Thomas, and Urbański, *J.*, 1947, 924; Urbański and Lipska, *Roczniki Chem.*, 1952, **26**, 182; Urbański, Kolesińska, and Piotrowska, *Bull. Acad. Polon. Sci., Cl. III*, 1955, **3**, 179; Gürne and Urbański, *ibid.*, p. 175; *Roczniki Chem.*, 1957, **31**, 855; Eckstein, Sobótka, and Urbański, *ibid.*, 1956, **30**, 133.

[2] Senkus, *J. Amer. Chem. Soc.*, 1950, **72**, 2967.

[3] Gürne and Urbański, *Bull. Acad. Polon. Sci., Cl. III*, 1956, **11**, 221; *Roczniki Chem.*, 1957, **31**, 869.

aqueous formaldehyde (0·15 mol., 15 ml.). Sodium hydrogen carbonate (0·5 g.) and freshly distilled *cyclo*hexylamine (0·1 mol., 9·9 g.) were added dropwise. The temperature rose by 10—15° and was kept at 60—65° for 3 hr., with stirring. The colourless resinous *oxazine* was washed with water, dissolved in hot ethanol, and left to crystallise (yield, 8·5 g., 33%). On repeated crystallisation from ethanol it formed needles, m. p. 55—57° (Found: C, 60·8; H, 9·8; N, 11·4. $C_{13}H_{24}O_3N_2$ requires C, 61·0; H, 9·5; N, 10·9%).

5-Butyl-3-cyclohexyltetrahydro-5-nitro-1 : 3-oxazine.—2-Butyl-2-nitropropane-1 : 3-diol (prepared from 1-nitropentane) (0·1 mol., 17·7 g.) with 30% aqueous formaldehyde (0·15 mol.) and *cyclo*hexylamine (0·1 mol.) in presence of hydrogen sodium carbonate (0·5 g.) gave, as above, the *oxazine* (14·5 g., 53%), needles, m. p. 57—59° (from alcohol) (Found: C, 62·2; H, 9·5; N, 10·8. $C_{14}H_{26}O_3N_2$ requires C, 62·3; H, 9·7; N, 10·4%).

Dipole Moments.—These were measured by the heterodyne-beat method, with benzene as a solvent, at 20°. The results were extrapolated by Le Fèvre and Vine's method. The experimental error was ±0·1 D.

The authors are much indebted to Professor W. Tomassi, Dr. H. Calus, and Miss H. Jankowska for measuring the dipole moments.

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383. 5- *and* 6-*Fluoro*-3-*indolylacetic Acid.*

By ERNST D. BERGMANN and ZVI PELCHOWICZ.

THE observations that 5-fluorotryptophan is an antagonist of tryptophan,[1] and 5-fluorotryptamine an antagonist of tryptamine,[2] led us to study the biological relation of 5- and 6-fluoro-3-indolylacetic acid to 3-indolyl-2-acetic acid (heteroauxin).

The two fluoro-compounds were synthesised by a conventional method:[3] the respective fluoroindoles were converted by formaldehyde and dimethylamine into 5- and 6-fluorogramine, and these compounds by potassium cyanide into the 5- and 6-fluoro-3-indolylacetonitrile, which were hydrolysed without isolation. The overall yields were 80%.

Preliminary experiments kindly carried out by Professor M. Evenari, Department of Botany, Hebrew University, have shown that the two compounds are germination-inhibitors.

Experimental.—5-Fluoroindole has been prepared by Allen, Brunton, and Suschitzky [4] from ethyl pyruvate *p*-fluorophenylhydrazone by Fischer's method, followed by hydrolysis and decarboxylation. We used Reissert's method.

5-Fluoro-2-nitrotoluene. 3-Methyl-4-nitroaniline, prepared [5] from *N*-acetyl-*m*-toluidine [m. p. 138° (from 50% ethanol)] (14 g.) was dissolved in hot concentrated hydrochloric acid (30 ml.), cooled in ice-salt, and treated with sodium nitrite (7·6 g.) in water (20 ml.). To the filtered solution, 50% fluoroboric acid (24 ml.) was added and the fluoroborate (11 g., 48%) filtered off, washed, and dried. It was mixed with half its quantity of talcum powder and decomposed in small batches at 100°. The product (30%), isolated by distillation with steam and extraction of the distillate with ether, boiled at 114°/30 mm. It has been obtained before by nitration of *m*-fluorotoluene.[6]

5-Fluoroindole-2-carboxylic acid. To a mixture of anhydrous ether (5 ml.) and anhydrous ethanol (10 ml.), potassium (3·2 g.) was added; when the reaction became slow, more ethanol (17 ml.) was added. After the metal had dissolved, the product was diluted with ether (125 ml.) and cooled, and successively ethyl oxalate (12·3 g.) and 5-fluoro-2-nitrotoluene (11 g.) were

[1] Bergmann, *Proc. k. ned. Akad. Wetenschap.*, 1954, *C*, **57**, 108; Sharon and Lipmann, *Arch. Biochem. Biophys.*, 1957, **69**, 219.
[2] Unpublished results from our laboratories.
[3] Snyder and Pilgrim, *J. Amer. Chem. Soc.*, 1948, **70**, 3770.
[4] Allen, Brunton, and Suschitzky, *J.*, 1955, 1283.
[5] Wibaut, *Rec. Trav. chim.*, 1913, **32**, 287.
[6] Schiemann, *Ber.*, 1929, **62**, 1794.

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added. A red solid slowly separated and was filtered off after 24 hr. and dried. This potassium 5-fluoro-2-nitrophenylpyruvate (15·5 g., 75%) was heated at 100° (reflux condenser) with 35% ammonia solution (150 ml.) and water (175 ml.), with stirring, and a solution of ferrous sulphate heptahydrate (157·5 g.) in water (175 ml.) was added. After a further hour's heating, the solution was filtered and acidified. The solid powder so obtained was filtered, dried, and recrystallised from 50% alcohol. The product melted at 233° (decomp.); Allen *et al.*[4] reported 248—249° (decomp.).

5-Fluoroindole. The ammonium salt of the foregoing acid was heated at 250° for 30 min. and the product isolated by steam-distillation. It formed colourless plates, m. p. 46° (lit.,[4] 46°) (20%) (Found: C, 71·2; H, 4·3. Calc. for C_8H_6NF: C, 71·1; H, 4·4%).

6-Fluoroindole. The Reissert synthesis was employed (cf. Allen *et al.*[4]). 4-Fluoro-2-nitrotoluene [8] (b. p. 107—109°/24 mm., 56—57°/0·2 mm.) was obtained, as described above, from 4-methyl-3-nitroaniline. 4-Fluoro-2-nitrophenylpyruvic acid, recrystallised from aqueous alcohol, melted at 135°, 6-fluoroindole-2-carboxylic acid, recrystallised from xylene, at 246° (lit., 246°), and 6-fluoroindole at 72° (lit., 75°).

5-Fluorogramine. An ice-cold solution of 25% aqueous dimethylamine solution (1·8 ml.), glacial acetic acid (1 ml.) and 40% aqueous formaldehyde (0·75 ml.) was added to solid 5-fluoroindole (1·25 g.), which dissolved quickly. After 24 hr. at room temperature, an excess of 10% aqueous potassium hydroxide was added, and the precipitate filtered off and recrystallised from acetone (yield quantitative; m. p. 139—141°) (Found: C, 68·5; H, 6·7; N, 14·3. Calc. for $C_{11}H_{13}N_2F$: C, 68·7; H, 6·7; N, 14·6%). Quadbeck and Roehm [8] report m. p. 145—146°.

6-Fluorogramine, obtained analogously and in the same yield, and recrystallised from acetone, melted at 131—132·5° (Found: C, 68·4; H, 6·6; N, 14·5%).

5-Fluoro-3-indolylacetic acid. To a solution of 5-fluorogramine (22 g.) in ethanol (250 ml.), a solution of potassium cyanide (44 g.) in water (70 ml.) was added and the mixture refluxed for 90 hr., neutralised with hydrochloric acid, and evaporated to dryness. The residue was refluxed for 4 hr. with 2N-potassium hydroxide (150 ml.), and the solution was acidified with dilute hydrochloric acid and thoroughly extracted with ether. The ether residue (17·5 g., 80%) was purified by dissolution in sodium hydrogen carbonate (charcoal) and acidification and eventually by recrystallisation from isopropyl alcohol. This *acid* had m. p. 140—141° (Found: C, 62·1; H, 4·0; F, 10·3; N, 7·6. $C_{10}H_8O_2NF$ requires C, 62·2; H, 4·3; F, 10·0; N, 7·3%).

6-Fluoro-3-indolylacetic acid, prepared in the same manner and in the same yield, had m. p. 165—165·5° (from isopropyl alcohol) (Found: C, 62·3; H, 4·0; F, 10·4; N, 7·3%).

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TEL-AVIV, ISRAEL.

[*Received, December 29th*, 1958.]

[7] Steck and Fletcher, *J. Amer. Chem. Soc.*, 1948, **70**, 439; Suschitzky, *J.*, 1953, **3326**.
[8] Quadbeck and Roehm, *Z. physiol. Chem.*, 1954, **297**, 229.